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DYNAMICS OF THE ACTION OF PENICILLIN IN EXPERIMENTAL ANIMALS

Observations on Mice

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IN THE last few years penicillin has established itself as a drug of great therapeutic value, possessing in a high degree the characteristics of an ideal antiseptic: exceedingly low toxicity and high bactericidal and bacteriostatic efficiency. The great demand for this drug in wartime and the early difficulties of large scale production made it imperative to use the minimal effective dosage. Arbitrary dosage schedules were selected by clinical trial and notable successes were achieved, but there is little evidence to show that the dosage used was optimal or even the most economical.

Early systematic studies[1] demonstrated that penicillin is rapidly excreted in the urine after parenteral administration. It has been generally accepted in the past that a sustained blood level of the drug is essential and, therefore, that it must be administered either continuously or at frequent intervals or that special methods must be used to retard its absorption or excretion.[2] There is, however, no good evidence that such maintenance of measurable blood levels is always essential, nor has the duration after infection of the action of the drug on the parasite population been determined.

The experimental work presented in this paper was designed to answer the following questions: 1. Can penicillin action be demonstrated in vivo only as long as measurable blood levels of the drug are present? 2. What is the effect on the therapeutic results of the length of the intervals between injections? 3. What is the optimum relationship between magnitude of dose and interval of time between injections? .

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1. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**:425, 1943.

2. (*a*) Romansky, M. J., and Rittman, G. E.: Method of Prolonging Action of Penicillin, Science **100**:198, 1944. (*b*) Rammelkamp, C. H., and Bradley, S. E.: Excretion of Penicillin in Man, Proc. Soc. Exper. Biol. & Med. **53**:30, 1943. (*c*) Beyer, K. H.; Woodward, R.; Peters, L.; Verwey, W. F., and Mattis, P. A.: Prolongation of Penicillin Retention in Body by Means of Para-aminohippuric Acid, Science **100**:107, 1944.

The clarification of these points seems worth while, for, in spite of the rapid advances being made at present in the development of penicillin for oral use, it is felt that parenteral administration will be utilized for some time in the treatment of severe infections. It is possible that on the basis of experimental work dosage schedules for penicillin treatment might be devised which could combine greater effectiveness than in the past with increased comfort for the sick. If, for example, larger doses at six hour intervals could be demonstrated to be as effective as smaller ones given three hours apart, such a development might materially benefit the patient.

In the experimental approach to this question it was first necessary to establish a laboratory "model" lending itself to the study of some of the factors involved. After preliminary standardization of a streptococcic infection in mice and its treatment with penicillin, the problem was attacked by two methods:

1. Observation of survival rates in animals treated with different amounts of penicillin with varying intervals of time between injections.

2. Study of the effects of parenterally administered penicillin on the bacterial population in the heavily infected host by means of cultures of tail blood, cultures of peritoneal fluid and bacteriologic autopsies.

METHODS

1. *Infection.*—A virulent beta hemolytic streptococcus, strain G22R (Lancefield group A, type 3), isolated from a patient with sore throat, was used as the infecting agent throughout all experiments. The average lethal dose was approximately 500 organisms injected intraperitoneally into white mice. The strain was maintained in the frozen state at -70 C. without change in virulence for nine months. The standard inoculum was prepared by subculturing 0.5 cc. of the thawed stock culture in 5 per cent horse blood broth for eight to ten hours at 37 C. Five-tenths cubic centimeter of this culture was transferred to ordinary meat extract broth, incubated for ten to twelve hours at 37 C. and then serially diluted in cooled broth blanks. The standard inoculum consisted of 0.5 cc. of a 1:1,000 dilution containing approximately 15,000 to 150,000 organisms injected intraperitoneally. Strain G22R proved to be highly sensitive to penicillin. Broth cultures of the streptococcus were regularly completely inhibited by 0.001 unit of penicillin per cubic centimeter.

2. *Experimental Animals.*—A uniform strain of white Swiss mice was used, the average weight being 15 to 22 Gm. Ninety-eight per cent of all untreated animals infected with the standard inoculum died within twenty-four hours.

3. *Penicillin.*—The sodium salt of penicillin was made up in solutions of the desired strength with sterile isotonic solution of sodium chloride. Blood levels of penicillin were determined by the method of Wolohan and Cutting [3] on whole citrated blood obtained by cardiac puncture of mice lightly anesthetized with ether.

3. Wolohan, M., and Cutting, W.: A Modified Method for Measurements of Penicillin Blood Levels, J. Lab. & Clin. Med. **30**:161, 1945.

4. *Treatment.*—The first injection of penicillin was always given four hours after infection, and subsequent treatments were given at intervals of from four to sixteen hours. An appropriate amount of the drug was contained in 0.2 cc., which was injected intraperitoneally or into the thigh muscle. After treatment, the mice were observed for seven days and deaths were noted. The cause of death was checked for about half the mice by culturing the heart blood.

5. *Cultures of Tail Blood.*—The tail was cleaned with dilute saponated solution of cresol and alcohol in the usual way; then it was cut with sterile scissors, and 2 drops of blood were streaked on a segment of a blood agar plate.

6. *Cultures of Peritoneal Fluid.*—At various intervals 1 cc. of sterile isotonic solution of sodium chloride was injected intraperitoneally and the abdomen massaged for one minute. Fluid was then withdrawn by capillary pipet, and 2 uniform drops were cultured on blood agar plates.

7. *Bacteriologic Autopsies.* — The method followed was essentially that described previously.[4] At various intervals after infection and treatment, small groups of mice were anesthetized with ether and autopsies were performed with sterile instruments under strictest aseptic precautions. Cultures were taken in the following sequence: (*a*) 2 drops of tail blood, obtained as indicated; (*b*) scrapings from the peritoneum and a loopful of peritoneal fluid, (*c*) lymph node juice (the para-aortic celiac lymph nodes were dissected out and squeezed and the juice plated); (*d*) uniformly cut surfaces of spleen and liver smeared over standard segments of blood agar plates, and (*e*) a large drop of heart blood. Occasionally bone marrow from the femur was also cultured. All cultures were made on 10 per cent horse blood agar plates, without penicillin inactivator, and incubated for twenty-four hours at 37 C. After incubation the plates were either sterile (occasional contaminants were present on the segments that had been touched with the cut tail) or showed the characteristic colonies of the streptococcus surrounded by a marked zone of hemolysis. Frequently one or more segments was completely hemolyzed, with confluent growth of the organisms. Results were recorded in the following terms: $0 =$ blood plate segment sterile; $1\text{-}35 =$ actual number of colonies of hemolytic streptococci counted per segment; $c =$ more than 35 colonies per segment or confluent growth. One cannot lay claim to absolute accuracy for this method, but its results have comparable value. Arguments for its validity have been presented elsewhere.[4]

RESULTS

1. *Blood Levels of Penicillin in Mice.*—After intramuscular or intraperitoneal injection of 30 units of penicillin into 20 Gm. mice absorption and excretion were very rapid, the curve of blood levels being similar to that observed for human beings.[1] Chart 1 indicates that one hour after injection 0.03 unit per cubic centimeter of whole blood was present. Twenty minutes later only traces of penicillin and fifty minutes later no bacteriostatic activity of the blood at all could be detected. Similar results were obtained with doses up to 150 units. It seems, therefore, that most of the injected penicillin was absorbed and excreted within eighty minutes after injection. Attempts to determine the actual amounts

4. Jawetz, E., and Meyer, K. F.: Behavior of Virulent and Avirulent P. Pestis in Normal and Immune Experimental Animals, J. Infect. Dis. **74:**1, 1944.
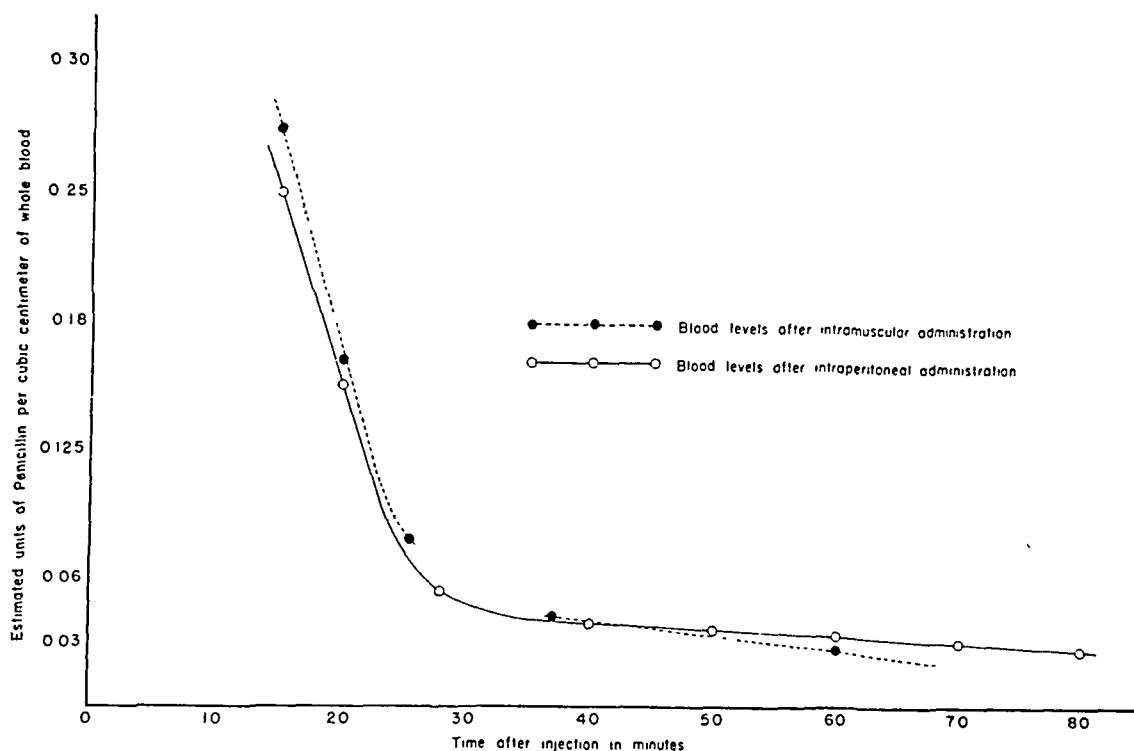
Chart 1.—Blood levels of penicillin in mice after intramuscular or intraperitoneal administration of 30 units.
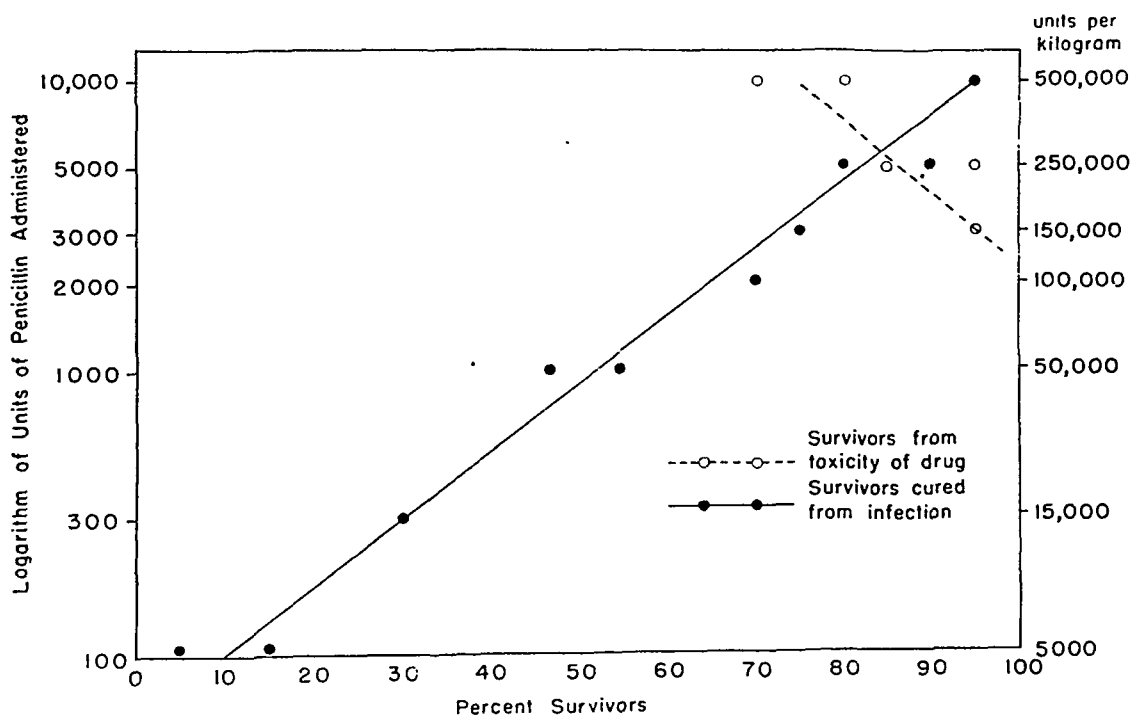
Chart 2.—Effect of large single doses of penicillin given intramuscularly on the rate of survival of mice from a severe streptococcic infection. Ninety-eight per cent of all controls die in eighteen hours.

excreted failed because of the great technical difficulty of quantitative collection of urine from small animals.

2. *Results of Penicillin Treatment Determined by Survival Rates.*— A. Effects of a Single Dose: As shown in chart 2, single doses of less than 50,000 units per kilogram of body weight given intramuscularly did not save more than 50 per cent of the animals. There appeared to be a linear increase in the survival rate with a logarithmic increase in the dose. Ninety-five per cent of the experimental animals that had survived the toxic impact of the injection were cured by a dose of 500,000 units per kilogram. Twenty to 30 per cent of the mice died from acute toxicity within ten to thirty minutes after injection of this amount of penicillin. Within five to eight minutes after treatment such animals had labored, gasping respiration, rapidly became prostrated and somnolent, with sunken flanks and great muscular weakness, and soon died in respiratory failure. No deaths from toxicity were observed with doses below 100,000 units per kilogram. It was uncertain whether the toxic effects were to be attributed to the active penicillin itself or to an impurity in the preparation.

B. Effects of Three Equal Intramuscular Injections Given Four Hours Apart: Again, a fair correlation was observed between the logarithm of the dose of penicillin and the survival rate, as shown in chart 3. In marked contrast to the experience with single doses, however, the amount of penicillin necessary was much smaller. Optimal results, or survival of more than 85 per cent of the animals, were obtained with 5,000 units per kilogram, and no toxicity was observed.

C. Effect of Three Injections of 30 Units·of Penicillin Each, Given Intraperitoneally or Intramuscularly, from Four to Sixteen Hours Apart: Representative results of a series of experiments are presented in table 1. Good results were obtained even when treatments were spaced

TABLE 1.—*Effect of Treatment with Three Equal Doses of Penicillin (30 Units Each) Administered at Various Intervals*

				Percentage of Survivors						
				Intraperitoneal Treatment:			Intramuscular Treatment:			
Experiment No.	No. of Mice per Group	Average Weight of Mice, Gm.	Dose per Kilogram, Units	Interval Between Injections			Interval Between Injections			Untreated Controls
				4 Hr.	8-10 Hr.	16 Hr.	4 Hr.	8-10 Hr.	16 Hr.	
5	20	22	4,100	80	40	30	65	55	20	0
6	20	16	5,600	85	85	60	90	80	70	5
7	20	15	6,000	90	80	55	90	95	60	0

eight to ten hours apart, provided the total dose was kept above approximately 5,000 units per kilogram. The rate of cure below this level was definitely unsatisfactory with intervals of more than four hours between
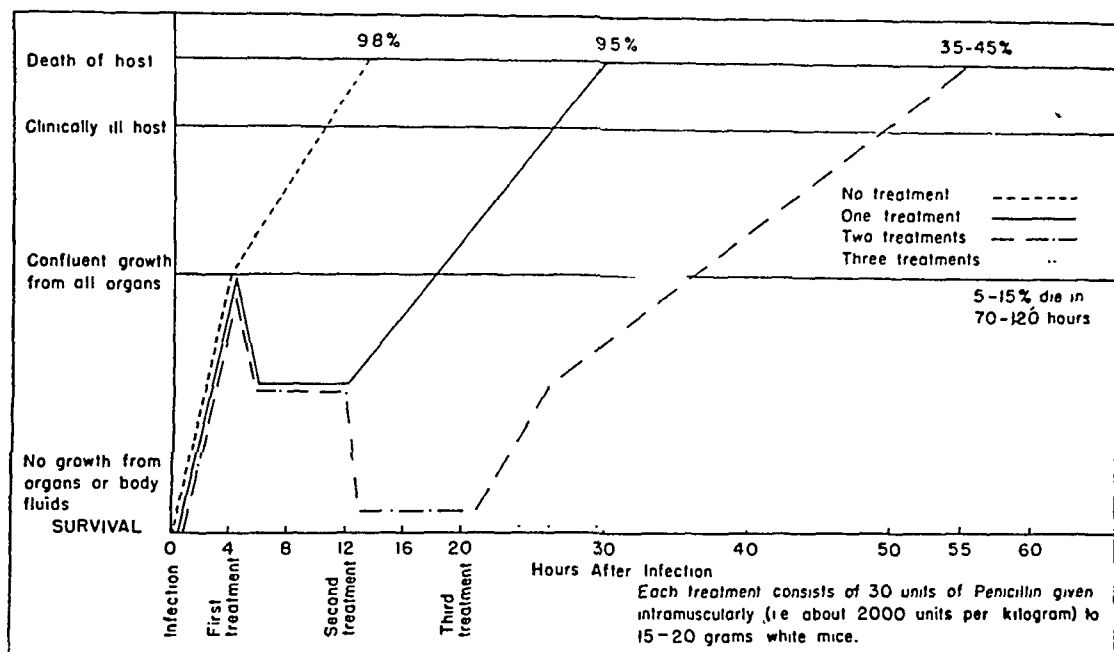
Chart 3.—Effect of three equal doses of penicillin administered intramuscularly at intervals of four hours on the rate of survival of mice from a severe streptococcic infection. Ninety-eight per cent of all controls die in eighteen hours. The logarithm of the total amount of penicillin administered is given on the ordinate.
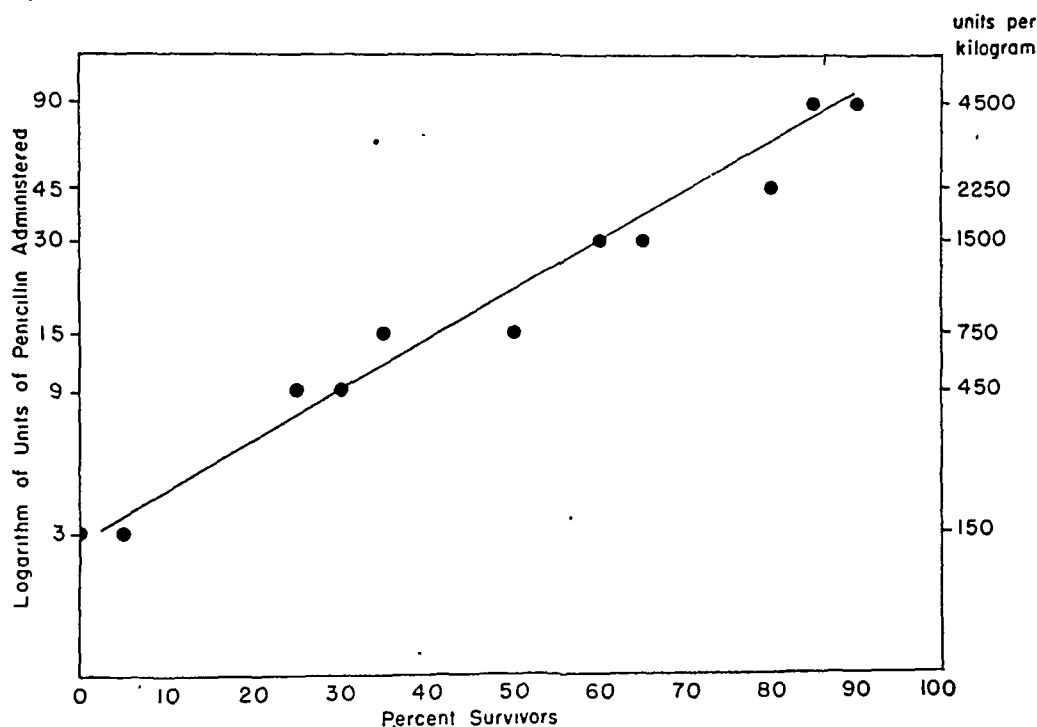
Chart 4.—Effect of penicillin on a severe streptococcic infection in mice. The chart is a composite schematic representation of the action of intramuscularly administered penicillin on the bacterial population in the host.

treatments. In addition to the saving of life, the survival time of animals dying in spite of treatment was greatly increased. Most controls died within eighteen to twenty hours after infection, whereas animals dying after treatment lived for an average of ninety hours.

D. Results of Postponing the Beginning of Treatment Until Symptoms Appear: As will be pointed out subsequently, the infecting organisms were disseminated very rapidly throughout the body of the host and were usually present in all organs three to four hours after inoculation. At that time no signs of infection were present and the mice appeared to be perfectly well. About eight or nine hours after infection the earliest lassitude and roughening of the fur was noticed and the peripheral blood contained many streptococci. Treatment started at this time prolonged life for forty-eight hours but never cured more than 10 per cent of the group, even when three doses of 100 units were given four-hours apart. This large amount of penicillin kept the peripheral blood free from organisms until shortly before death but apparently was unable to restore the activity of the animal's impaired defense mechanism.

TABLE 2.—*Comparison of the Effects of One, Two and Three Doses of 30 Units of Penicillin Given Intramuscularly 8 Hours Apart*

Experiment No.	No. of Mice per Group	Average Weight of Mice, Gm.	Percentage of Survivors			
			No Injection	One Injection	Two Injections	Three Injections
1	20	17	0	5	60	85
2	20	19	0	10	55	90
3	16	16	6	0	62.5	87.5

E. Relative Effect of One, Two and Three Injections of 30 Units of Penicillin Each: After it was observed that three injections of penicillin commonly cured all, and one injection none, of the animals, it became imperative to determine just where in the treatment the maximal effect was achieved. Suitable experiments, as shown in table 2, indicate that apparently the second injection most significantly raised the rate of cure while the third dose seemed to tip the balance for only a small number of the animals. These tests purposely were carried out with intervals of eight hours between treatments in order to demonstrate more precisely minor differences which might be hidden by overlapping effects of doses given only a short time apart.

3. *Cultures of Tail Blood.*—Cultures of the tail blood of untreated mice were always positive for streptococci six to eight hours after inoculation. Injection of penicillin at a time when many streptococci were were present in the peripheral blood usually cleared the blood stream but rarely cured the mice. A single dose of 30 units of penicillin usually kept cultures of tail blood sterile for twenty to thirty hours and until *four to*

eight hours before death. This apparent sterilization of the blood stream had no prognostic significance and could not be used as a guide to therapy. Probably the penicillin enabled the filtering organs (spleen, liver and bone marrow) to retain streptococci efficiently until overwhelming toxemia set in.

4. *Cultures of Peritoneal Fluid.*—Two objections militate against the use of this method. Repeated punctures of the abdominal cavity were certain to produce serious injury and thereby impair the animal's general resistance. In addition, the local trauma produces inflammation, outpouring of fibrin and fixation of bacteria. Thus one might expect to find apparent sterility of the peritoneal fluid due to the firm fixation of organisms in the fibrin meshes on the serous surfaces. Keeping these pitfalls in mind, one may summarize the essential results obtained by this method as presented in table 3 as follows: There was no striking disappearance

TABLE 3.—*Cultures of Peritoneal Washings*

Time, Hr.	No Injection: Mouse No. 1	2	3	4	One Injection: Mouse No. 5	6	7	8	Two Injections: Mouse No. 9	10	11	12	Three Injections: Mouse No. 13	14	15	16
0	Infected				Infected				Infected				Infected			
2	c	c	c	c	c	c	c	8	c	5	c	c	20	c	10	c
4	c	20	c	c	Treated				Treated				Treated			
5	c	c	30	c	c	35	c	c	c	20	35	c	12	c	c	14
7	c	c	c	c	c	20	10	c	—	—	—	—	4	30	c	c
9	c	c	c	c	c	15	c	c	26	30	c	8	—	—	—	—
11	25	c	c	35	—	—	—	—	c	13	c	20	30	14	c	29
12	—	—	—	—					Treated				Treated			
13	c	c	c	c	c	20	35	35	c	0	30	0	20	2	c	0
15	c	c	+	c	c	11	3	25	30	0	c	0	0	0	c	0
19	+	c	—	+	c	c	0	c	c	0	35	0	0	0	0	10
20	—	—	—	—	—	—	—	—	—	—	—	—	Treated			
21	—	c	—	—	c	c	c	c	30	0	20	0	0	0	0	0
25	—	+	—	—	+	c	+	c	c	0	22	0	0	0	10	0
30	—	—	—	—	c	+	—	c	+	8	c	c	0	0	c	0
40	—	—	—	—	—	—	—	+	—	0	c	+	0	0	c	0
50	—	—	—	—	—	—	—	—	—	0	+	—	0	+	—	0
60	—	—	—	—	—	—	—	—	—	S	—	—	S	S	—	S

Meaning of symbols: Infected = standard inoculum intraperitoneally; treated = 30 units of penicillin intramuscularly; c = confluent growth, or more than 35 colonies with hemolysis on plate; 1-35 = number of colonies with hemolysis counted on plate; — = not tested; + = animal died; S = animal survived.

of streptococci after the first intramuscular dose of 30 units of penicillin but only a slight reduction in number lasting for eight to twelve hours. The second injection, four to eight hours after the first, produced a significant drop in bacterial count which persisted for ten to fifteen hours. Gradually the streptococcic population returned in most animals, reaching its former level about twenty hours after the second injection. The third dose of the drug usually brought about the complete and permanent disappearance of bacteria from the peritoneum.

5. *Bacteriologic Autopsies.*—From previous experience [4] it appeared likely that the systematic survey of the bacterial population in the body of the host would give the most balanced and most reliable information

about the influence of penicillin on the course of the infection. Consequently, a number of experiments were performed with this technic. Tables 4 and 5 are sample protocols representative of the results obtained. A summary of the more important observations follows.

A. Normal Course of the Infection: Within three to four hours after inoculation, there was confluent growth of the cultures from peritoneum, celiac lymph nodes (draining the peritoneum), spleen and liver and usually from heart blood. Only occasional organisms could be recovered from the tail blood, and the animals appeared clinically well. Six to eight hours after infection the first signs of illness were noted and increasing numbers of bacteria were present in the tail blood; the celiac nodes were somewhat enlarged, and the peritoneal exudate was viscid. Nine to eleven hours after inoculation the mice were seriously ill and listless, the celiac nodes were more enlarged and the spleen was slightly enlarged. From then on the animals deteriorated rapidly and died in twelve to twenty hours. Throughout the illness all internal organs and the bone marrow yielded innumerable streptococci on culture.

B. Infection Modified by Intraperitoneal Penicillin Treatment: Within two hours after injection intraperitoneally of 30 units of penicillin there was a pronounced reduction of the bacterial growth from all organs. Growth on cultures of the organs remained at a low level for six to nine hours, then gradually increased until death. The tail blood remained sterile for eight to twelve hours after treatment and became positive for streptococci only as signs of illness appeared.

A second injection of the drug, given four to eight hours after the first, further reduced the number of streptococci, so that some animals appeared "sterilized" while others showed bacteria only in the spleen or liver. This marked depression of the bacterial population lasted for six to eighteen hours; then proliferation again started throughout the body. A third injection given during this period of depression usually cleared the host permanently.

C. Intramuscular Treatment: The effects of the first intramuscular dose of 30 units were usually much less dramatic than those with intraperitoneal treatment. Only slightly fewer bacteria could be recovered for six to nine hours than before treatment. The second dose during this period produced a sudden clearing of the body, lasting for eight to twelve hours. Some animals went on to permanent recovery, but most showed a return of the bacterial population. If a third injection was given during this depression, there was a rather gradual disappearance of streptococci over a period of hours. Sometimes a few organisms could be isolated from the spleen or liver as late as twelve to eighteen hours after the third dose; yet most of the control animals survived. This probably indicated that penicillin reduced the number of bacteria considerably and kept them

TABLE 4.—*Bacteriologic Autopsies: Effect of Intraperitoneal Injections of Penicillin*

Time, Hr.	No Treatment (Control) — Infected						One Treatment — Infected / Treated						Two Treatments — Infected / Treated						Three Treatments — Infected / Treated					
	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood
0	c	c	25	c	8	0	c	c	c	c	12	0	c	c	20	16	0	0	8	30	12	c	17	2
2	20	c	c	10	0	0	c	c	c	c	9	1	c	c	c	c	c	3	c	c	c	c	c	0
	c	c	c	c	20	1	5	0	25	5	23	0	c	30	15	c	30	0	c	c	c	c	14	0
4	c	c	c	c	c	5	c	0	20	5	0	0	0	0	1	0	0	0	1	0	5	25	0	0
	c	25	c	c	c	1	7	20	25	c	0	0	7	24	5	19	1	0	0	0	0	0	0	0
5	c	c	c	c	c	0	0	0	0	0	0	0	0	0	1	17	0	0	0	1	10	23	0	0
	c	c	c	c	6	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	30	c	c	c	21	25	2	2	6	15	15	0	0	0	0	0	4	0	1	1	2	5	5	0
	c	c	c	c	c	0	15	0	8	19	20	0	20	10	30	21	0	0	10	9	11	3	0	0
8	—	—	—	—	—	—	20	30	10	28	11	1	0	0	1	4	1	0	1	5	25	3	0	0
9	c	c	c	c	c	c	1	c	c	c	c	0	0	0	0	0	0	0	0	0	0	0	0	0
	c	c	c	c	c	35	0	17	15	21	c	0	7	23	5	23	2	0	0	0	0	0	0	0
11	c	c	c	c	27	4	25	30	30	20	25	1	15	35	9	35	4	0	0	0	0	3	5	0
	c	c	c	c	c	c	4	10	c	c	18	8	0	0	8	10	3	0	0	0	0	0	0	0
12	30	c	c	c	c	30	20	30	30	20	30	20	15	29	8	26	21	2	0	0	0	0	0	0
13	c	c	Dead	c	c	11	c	10	c	c	c	c	0	0	0	3	0	17	0	0	0	0	0	0
15	c	c	Dead	c	c	c	c	c	c	c	c	c	10	c	c	c	c	c	0	0	0	0	0	0
24	—	—	—	—	—	—	9	c	c	c	c	c	c	c	c	c	c	c	0	0	0	0	0	0

Meaning of symbols: see table 3.
Treatment: 30 units penicillin intraperitoneally at four hour intervals.

TABLE 5.—*Bacteriologic Autopsies: Effects of Intramuscular Injections of Penicillin*

Time, Hr.	No Treatment (Control)						One Treatment						Two Treatments						Three Treatments					
	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood
0.........	c	c	c (Infected)	c (Infected)	c	20	c	15	25 (Infected)	c (Infected)	20	1	24	4	25 (Infected)	30 (Infected)	2	1	35	20	20 (Infected)	10 (Infected)	3	0
4.........	c	c	c	c	c	c	12	30	c	c	18	1	20	35	c	30	c	0	4	2	21	29	16	3
5.........	c	35	c	c	c	25	27	10	c	c	9	0	26	c	20	c	c	3	10	10	35	c	6	0
8.........	20	c	c	c	c	3	3	20	15	15	3	0	7	11	c	25	15	10	c	c	c	c	15	2
....	c	c	c	c	c	c	c	3	8	8	1	0	c	17	c	c	14	0	c	5	3	c	5	0
11.........	30	25	c	c	20	25	10	c	7	4	3	1	21	8	30	35	15	3	c	20	c	15	20	1
12.........	c	c	Dead	Dead	20	c	8	c	c	c	20	10	c	4	20	5	c	0	10	21	12	c	c	3
13.........	c	c	Dead	Dead	c	2	20	c	32	c	30	5	7	4	20	(Treated)	1	0	2	9	(Treated)	4 (Treated)	1	0
15.........	—	—	Dead	—	—	c	c	12	c	28	20	0	2	8	20	14	3	0	5	c	30	1	4	0
....	c	c	c	c	c	9	12	35	21	20	14	2	0	1	2	1	0	0	0	c	1	0	0	0
19.........	c	c	c	c	c	(	10	24	c	c	1	0	0	0	2	25	1	0	4	20	4	8	0	0
20.........	—	—	—	—	—	—	19	c	c	c	30	2	15	11	21	0	4	0	3	c	c	c	7	16
21.........	c	c	—	—	c	16	8	c	c	c	c	1	9	22	15	13	10	1	0	3	15	4	10	0
25.........	c	c	c	c	c	c	c	c	c	c	c	0	0	0	0	31	0	0	7	2	21	7	4	0
....	c	c	c	c	c	c	c	c	Dead	Dead	c	9	20	26	0	0	0	0	0	19	34	16	5	1
40.........									Dead	Dead			10	4	31	c	c	0	0	0	0	0	0	0

Meaning of symbols: see table 3.
Treatment: 30 units penicillin intramuscularly at eight hour intervals.

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at a low level for some time, permitting the normal body defense mechanisms to dispose of the few stragglers.

The question was also investigated as to whether the mice acquired some degree of immunity during their brief illness. If so, the final clearance of the body might be due to immune reactions rather than to normal body defenses. To clarify this question, groups of normal unused mice were compared with groups that had been cured twice of their infection by treatment with penicillin. As seen in table 6, no significant increase in

TABLE 6.—*Comparison of the Resistance to Streptococcic Infection of Normal and of Twice Exposed Mice*

Experiment Number	Animals per Group	Percentage of Survivors	
		Normal Mice	Twice Exposed Mice
1...............................	50	2	8
2...............................	40	0	2.5

resistance could be found in the twice exposed mice. Admittedly, however, this test may have been too stringent to detect minor differences in acquired immunity.

COMMENT

The results obtained in this study indicate quite definitely that the success of parenteral penicillin therapy for mice depends on both the quantity of penicillin administered and the interval between injections. Small amounts had to be given very frequently in order to save a significant portion of infected animals, but if large doses were used injections could safely be spaced eight to ten hours apart and excellent results obtained. A single injection sufficed to cure the majority of animals when very large doses of penicillin were used, whereas with small amounts frequently repeated administration was necessary.

It could be shown definitely that the effects of penicillin on the bacterial population in the host lasted much longer than the measurable blood levels. The latter persisted for only about one hour after the injection of penicillin, while the depression of the bacterial population continued for six to eight hours or longer. The final clearance of streptococci from the body, occurring often many hours after the last injection of penicillin, probably may be ascribed to normal body defense mechanisms. No significant immunity could be demonstrated in surviving experimental animals cured by the drug. The prolonged inhibition of bacterial proliferation in the absence of significant blood levels of penicillin must be attributed to one or more of the following mechanisms:

A. Presumably most of the penicillin circulating in the blood stream during the first hour after administration is excreted through the kidneys. It is possible, however, that very minute quantities remain in the tissues

and are sufficiently bacteriostatic to prevent free multiplication of bacteria. The cures obtained with very large single doses of penicillin might be due to failure of rapid tubular excretion with longer maintenance of significant concentrations of penicillin in the tissues.

B. The first impact of high penicillin levels shortly after administration. may either kill a large proportion of the original streptococcus population or else so damage their enzyme systems that multiplication is severely inhibited for several hours.

C. The early high penicillin levels may injure the micro-organisms in such a way as to make them much more accessible to the normal body defenses, especially phagocytosis and filtration. Thus the host is able to cope effectively with relatively large numbers of bacteria for several hours.

Quite certainly the filtration mechanism of liver, spleen and bone marrow is much more efficient for many hours after the injection of penicillin. This probably explains the frequently negative results of culture of peripheral blood in spite of abundant growth of streptococci from all internal organs. "Sterilization of the blood stream," measured by culture of peripheral blood after penicillin treatments, seems to have no prognostic value whatever and is merely the result of improved retention of·bacteria by the blood-filtering organs.

It was felt that it was possible, by combining the significant results of this study, to draw up a schematic representation of penicillin action as observed in mice. Chart 4 demonstrates that untreated animals harbor many streptococci in all organs four hours after infection, become ill six to eight hours later and succumb to the infection to within twelve to twenty hours. One intramuscular injection of penicillin four hours after inoculation produces a moderate fall of the bacterial population, which is maintained at an intermediate level for six to eight hours but then rapidly increases, so that 95 per cent of the animals are dead in thirty hours. Thus, up to a dose of 5,000 units per kilogram the first injection never cures. It fails to reduce the number of bacteria to levels susceptible to the normal clearing mechanism of the body. With larger doses, as shown in chart 2, this may occasionally occur, but 50,000 units per kilogram is required to cure 50 per cent of the mice with a single injection. Ten times that dose kills 20 to 30 per cent of the animals by immediate toxicity but cures all others. If one assumes' that the toxicity is due to contaminating materials rather than to the active principle of the drug, it may conceivably be possible safely to treat and cure an acute streptococcic infection with a single large dose given intramuscularly (e.g., about 40,000,000 units for a man of 70 Kg.).

If a second dose of penicillin is administered at any time during the "depressed level" following the first injection, there is a rapid, marked ·drop of bacterial counts to a lower plane. Many animals are apparently

able to destroy the remaining organisms, for over 50 per cent remain cured after the second injection. The rest die in an average of fifty-five hours. The injection of a third dose during the second depression assists the body defenses in the control of the residual organisms and permits the cure of the majority of animals. Occasionally no bacteria can be recovered for twenty hours after the third dose of penicillin, but later they reappear and kill 5 to 15 per cent of the mice.

The importance of the size of the dose of penicillin in the treatment of experimental animals has been established. It was clearly shown that the rate of survival of treated animals was directly proportional to the amount of penicillin administered per dose. When larger doses were given, fewer injections were necessary and longer intervals between injections were permissible with satisfactory results. There was no "upper limit" of the useful dose of penicillin except that imposed by toxicity phenomena. With very large doses, exceeding 50,000 units per kilogram, more than half of the animals—that would all have died if untreated—could be saved by a single injection of the drug, without resort to "absorption-slowing" devices. With 100,000 to 150,000 units per kilogram, just below the minimal toxic dose, about 75 to 85 per cent of the animals are cured by a single injection, while 98 to 100 per cent of the controls die.

These figures seem sufficiently impressive to warrant serious consideration in clinical medicine. While, obviously, no results obtained on mice can be applied to human beings, it may be of considerable interest to speculate about the possible clinical implications of this experimental work. If penicillin action lasts as long in persons as it does in mice, it may be quite permissible to give injections to patients six to eight hours apart. At the same time the daily dose would have to be kept above 5,000 units per kilogram, or approximately five times the minimal inhibiting dose in vitro, since it was at this level only that the long intervals were as satisfactory as shorter ones. It would seem advisable to give larger amounts of the drug to all patients now that supplies are no longer restricted and the cost is not prohibitive. The striking cures obtained with very large single doses in mice certainly suggest their trial in human disease. There appear to be no contraindications to very large doses that do not exceed the toxic level of the preparation used. The sensitivity phenomena are probably not influenced by dosage and are rarely significant. Clinical trial of doses between 20,000 and 100,000 units per kilogram per day seems indicated, not only for chronic infections with organisms partly resistant to penicillin, such as subacute bacterial endocarditis, but also for malignant acute infections. The safety factor and ease of cure would thereby be greatly increased without significant dis-

advantage. Recent reports [5] indicate that the so-called "standardized" treatment schedules may be entirely inadequate for the control of infections caused by penicillin-sensitive organisms, producing bacteriologic remissions rather than cures.

The success obtained in our studies with high doses administered in short courses at intervals of six to eight hours between injections might also encourage clinical trial of relatively few large doses spaced six to eight hours apart in treatment of other bacterial infections besides gonorrhea and meningococcemia.[6] If successful, such trials may provide the basis of new, more convenient and safer methods for parenteral penicillin treatment. Experiments are in progress on experimental animals and in clinical trial to determine such optimal dosage schedules.

SUMMARY

From a study of the effects of penicillin in treatment of a severe hemolytic streptococcus infection in mice the following observations were made:

1. The success of penicillin by parenteral injection against an otherwise fatal infection of mice depended on both the quantity of penicillin administered and the interval between injections.

2. Small doses of the drug had to be given frequently (every four hours) in order to save a significant portion of infected animals, but if large doses were used injections could safely be spaced eight to ten hours apart with excellent results.

3. With very large doses a single injection sufficed to save a majority of animals.

4. By means of several bacteriologic methods it was demonstrated that the effects of penicillin on the bacterial population in the host lasted much longer than the measurable blood levels.

5. An attempt was made to elucidate the dynamics of a curative course of penicillin in mice. The possible clinical implications of the experimental results were discussed.

5. Lapenta, R. G.; Weckstein, A. M., and Sarnoff, H.: The Inadequacy of a Standardized Dosage of Penicillin, J. A. M. A. **128**:168 (May 19) 1945.

6. Anderson, D. G.: The Treatment of Infections with Penicillin, New England J. Med. **232**:400, 1945.

VENOSPASM

Its Part in Producing the Clinical Picture of Raynaud's Disease

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ALTHOUGH many hundreds of papers have been written on Raynaud's disease, there is still no clearcut clinical concept of the mechanism involved nor an explanation for the varied pictures which are all classified under the term. The problem has been further complicated by the introduction of the term "Raynaud's phenomenon," since there is no agreement as to just what differentiates Raynaud's disease from Raynaud's phenomenon. The modern concept of Raynaud's disease which has been generally accepted is that the attack of dead whiteness in the fingers or cyanosis is due to a local fault in digital or palmar arteries, so that they constrict abnormally to cold and with nervous tension. Certain observations that we have made led us to doubt that arterial spasm can explain the entire picture of Raynaud's disease. These observations have enabled us to separate patients with the syndrome into several groups on the basis of their clinical behavior and have added clarity to our diagnosis and treatment, since we are now able to classify each patient into one or another of the groups described later, depending on which part or parts of the vascular tree must be involved to produce the clinical picture.

Our interest in the problem of Raynaud's disease and Raynaud's phenomenon was stimulated by studies on a patient who previously had been given a diagnosis of "cold allergy" and who had also received the diagnosis of Raynaud's disease. This patient, a white man aged 26, experienced swelling and cyanosis of the hands and face on exposure to cold. A basal vascular tone test[1] done by us revealed that this patient's digital arteries had a low grade of tone, since they did not constrict to cold for at least one hour, the temperature of the fingers remaining above 30 C. (86 F.) in a room in which the temperature was controlled at 20 C. (68 F.). This response is characteristic of

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1. Naide, M., and Sayen, A.: A Test for Vascular Tone in Humans and Its Application to the Study of Vascular Diseases, with Special Reference to the Etiology and Prevention of Thrombophlebitis, Am. J. M. Sc. **207**:606, 1944.

a person with relaxed arteries. At the same time it was observed that the veins became invisible with exposure to cold and the hands commenced to swell and to become cyanotic. It then occurred to us that this patient's symptoms could be explained as due to venospasm. It appeared that this might be an aberrant form of Raynaud's disease, in which abnormal constriction on exposure to cold was taking place in the veins instead of in the arteries. Subsequent measurements of the patient's venous pressure while he was exposed to cold showed the veins to be in spasm. Since nothing was apparently abnormal in the arteries, our attention became focused on the veins. While the patient was cold we attempted to measure the venous pressure in the arms. We tested the pressure in three veins in both arms, and each time it appeared that the vein was undergoing spasm. No change in pressure occurred, although, with the needle still in the vein, when a tourniquet was applied above the needle the water in the manometer rose. When the patient was warmed, the venous pressure was easily measured, and it was found to be 110 mm. of water.

Study of this patient led us to the realization that the cyanosis and swelling were similar in character to such changes that we had seen in some patients with Raynaud's disease. It seems that the signs in these patients could be explained only on the basis of venospasm as well as arterial spasm. In further observations on a group of ·10 patients with Raynaud's disease and 4 patients with Raynaud's phenomenon we found that there were striking individual differences in their behavior during the attacks. In some of the patients there were signs of only arterial spasm, while in others there was clinical evidence of both arterial and venous spasm. Arterial spasm predominated over venospasm in some patients; in others the veins were the principal site of constriction.

Since the work of Lewis [2] and Landis,[3] spasm of the veins has been excluded as the principal factor in producing the clinical picture of Raynaud's disease in some patients. It is this failure to include the venous side of the vascular tree in Raynaud's disease which has created the present confusion concerning this disease, since it is impossible to explain the clinical picture in some patients by arterial spasm alone.

Some patients had only blanching of the fingers during the attack, with or without cyanosis but with visible veins on the dorsa of the

2. Lewis, T.: Experiments Relating to Peripheral Mechanism Involved in the Spasmodic Arrest of Circulation in the Fingers: A Variety of Raynaud's Disease, Heart **15**:7-101, 1929.

3. Landis, E. M., Jr.: Micro-Injection Studies of Capillary Blood Pressure in Raynaud's Disease, Heart **15**:209-228, 1930.

hands. Others had swelling and cyanosis of the fingers, as well as blanching, and in these the veins were invisible. The fingers of some began to appear puffed and cyanotic before blanching, suggesting that the veins were constricting before the arteries. All patients showed these phenomena in varying degree during an attack. In some of the patients the pain or discomfort accompanied arterial constriction. In other patients the pain and discomfort were associated only with the period of relaxation of arterial spasm. In the latter group pain was not associated with the vasoconstriction.

Again, it appeared that the difficulty in explaining these striking differences in the behavior of patients with Raynaud's disease had been due to failure to recognize that in some patients the symptoms are principally due to the fact that the veins are more readily constricted than the arteries. Also, it has not been recognized that in some of these patients the veins remain constricted while the arteries are relaxing, thus creating a state of vascular congestion. This explains the onset of puffiness as well as discomfort in the fingers in this group of patients during a period of arterial relaxation. This is only to be expected, since vessels that constrict more readily to a stimulus, as do the veins in this group of patients, not only constrict first but on removal of the stimulus relax last.

Although the walls of veins are thinner than the walls of the corresponding arteries, veins also are richly supplied by sympathetic nerve fibers.[4] The smooth muscle of the veins responds to nervous stimuli in the same manner as does the smooth muscle of arteries. Franklin's "Monograph on Veins," gives in detail the large body of experimental and clinical evidence demonstrating the important influence of the nervous system on the venous system. In 1839 Valentin [4] demonstrated contraction of the horse's abdominal vena cava by stimulation. Gobler [4] in 1850 found that under appropriate conditions the veins on the dorsum of the human hand responded to a tap by contraction. It was in 1864 that Goltz [4] showed the relationship of the nerves to the veins. Many physiologists have demonstrated and described the responses of both the superficial and the deep venous systems of the extremities to nervous stimuli.

Lewis and Landis during the years from 1929 to 1934, presented evidence that the attack of dead whiteness in the fingers or of cyanosis is due to a local fault in the wall of small arteries only, the digital and palmar arteries, so that they constrict abnormally in response to cold and to emotional upsets. They attempted to establish the fact that the veins do not participate in the abnormal vasoconstriction. Lewis [2]

4. Franklin, K. J.: A Monograph on Veins, Springfield, Ill., Charles C Thomas, Publisher, 1937.

discussed the observations of Weiss [5] and Barlow,[6] who presented clinical evidence that there is abnormal contraction in the veins.

Because our observations were so contrary to those of Lewis and of Landis we analyzed their evidence for concluding that only arterial spasm occurs in Raynaud's disease and that obstruction to venous outflow is not present. We reinterpreted their findings in the light of what we were seeing and in the light of what has been discovered concerning vein reflexes since their work done in 1930. We arrived at the conclusion that their own observations not only do not exclude venospasm but are compatible with its presence in Raynaud's disease.

Lewis dismissed Weiss's [5] conclusion that the veins participate in the abnormal vasoconstriction of Raynaud's disease. Lewis, to rule out the presence of venospasm, described 6 cases in which, he stated, the cyanosis of the fingers was replaced by blanching immediately after elevation of the extremities and again recurred after the extremities were dependent. This indicated to him the presence of patent venous channels in the arm and hand. To us, these observations could also be explained by the action of a vascular stretch reflex, as described by Doupe and others.[7] By this mechanism, elevation of the arms would cause a drop in venous pressure, removal of the stretch reflex and, therefore, venous relaxation, with relief of the cyanosis. If the arm should be returned to a dependent position, the stretch reflex would come into play again as a result of increased venous pressure. This would bring on venous constriction and would reestablish the cyanosis.

Although blood flow is greatly reduced, there is always sufficient arterial inflow in these patients to maintain the cyanosis. This explanation was not available to Lewis, since these vein reflexes were not described until a number of years after his investigations of Raynaud's disease.

Landis, in his microinjection studies of capillary pressure in Raynaud's disease,[8] stated that venospasm is not a factor in Raynaud's disease, as the capillary pressure in the fingers rises very little and very slowly in response to venous congestion induced by an increase in venous pressure as the result of a cuff around the upper part of

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5. Weiss, M.: Ueber symmetrische Gangrän, Wien. Klinik **8**:346, 1882; Ueber Venenspasmus, Wien. med. Presse **23**:988, 1015, 1045 and 1095, 1882.

6. Barlow, T.: Three Cases of Raynaud's Disease, Tr. Clin. Soc. London **22**:413, 1888-1889; Some Cases of Raynaud's Disease, Illust. M. News **3**:73, 97, 125 and 176, 1889.

7. Doupe, J.; Robertson, J. S. M., and Carmichael, E. A.: Vasomotor Responses in the Toes: Effect of Lesions of the Cauda Equina, Brain **60**:281, 1937.

the arm. This phenomenon can as well be evidence of a mechanism at work during venospasm. If the veins are in spasm at the wrists, back pressure cannot be transmitted to the fingers from the brachial veins except through the venous plexus. Landis has stated that transmission of venous pressure to capillaries through these plexuses will cause but a small rise in capillary pressure in patients with Raynaud's disease. It is just such a small rise, 5 to 8 mm. of mercury, that he observed in a patient with Raynaud's disease, indicating that the transmission of back pressure from the arm to the fingers in his patient may have been referred only through these plexuses, the veins already being in spasm between the point of increased pressure and the capillaries of the cyanotic fingers. The fact that many patients do not have relief from venous spasm until after arterial spasm has ceased could also explain the appearance of slight swelling that was noted by Landis in the fingers during recovery from arterial spasm; this swelling he ascribed to "changes in fluid balance consequent upon asphyxia of the capillary wall and upon the increased capillary pressure." Landis also described a rise in capillary pressure during "the hyperemia" of recovery. Such a rise can be readily explained by venospasm causing engorgement of the capillaries, as in this phase arterial inflow would be continually increasing in the presence of a restricted outflow, although Landis chose to attribute this to capillary engorgement due to anoxia. However, as we have seen in a nonvasospastic but ischemic extremity, this swelling is not present, despite the appearance of rubor and capillary engorgement. Furthermore, these capillary studies do not explain the puffed fingers or hands at the beginning of an attack in some patients or the "puffed hands" that are present in others all winter.

Of the 10 patients with Raynaud's disease seen by us, the clinical features in only 1 were those produced by arterial spasm alone; in 8 both venospasm and arterial spasm were required to produce the picture and in 1 venospasm alone was present. The last was the patient with so-called cold allergy. The ages of the 10 patients ranged from 28 to 62 years; 9 were female and 1 was male. Necrosis of finger tips was present only in the group with both venous and arterial spasm. The probable explanation for this is that venous stagnation favors ulceration, just as it does in a leg with varicose veins or with thrombophlebitis.

In the 4 patients with Raynaud's phenomenon, the symptoms were part of a generalized scleroderma. In 2 of these patients there was evidence of both venous and arterial spasm, the veins being invisible and cyanosis and increased swelling being present when the patient was exposed to cold.

The following observations were made concerning the patients with both venospasm and arterial spasm:

1. The fingers of both hands blanched on exposure to cold or in response to emotional tension.

2. There was a history of puffed or swollen hands throughout the winter, in addition to blanching and cyanosis.

3. There was an appearance of cyanosis and swelling before blanching in some patients.

4. Fingers were puffed during as well as between attacks.

5. Increased swelling followed the termination of attacks.

6. Veins on the dorsa of the hands were invisible or inconspicuous during exposure to cold and in most of these patients even during exposure to warmth.

On the basis of our observations we formulated the following classification which includes all the characteristic clinical pictures seen in patients with Raynaud's disease and Raynaud's phenomenon. It is obvious that the clinical picture will vary depending on the intensity of constriction in arteries and in veins and on the type of vessel in which abnormal constriction predominates.

Classification of Raynaud's Group of Vasospastic Disorders
(Bilateral, Symmetric, Digital Involvement)

1. Arterial spasm (or predominantly arterial) ; blanching, with or without cyanosis (no swelling)
    (a) Raynaud's disease: arterial (primary—no obvious cause)
    (b) Raynaud's phenomenon: arterial (secondary—due to other conditions)
2. Arterial and venous spasm (mixed) ; blanching, cyanosis and swelling
    (a) Raynaud's disease: arterial and venous (primary—no obvious cause)
    (b) Raynaud's phenomenon: arterial and venous (secondary—due to other conditions)
3. Venospasm (or predominantly venous) ; swelling and cyanosis (blanching absent or slight)
    (a) Raynaud's disease: venous (including some cases of "cold allergy")

REPORT OF CASES

CASE 1.—*Raynaud's disease; mixed venospasm and arterial spasm.*

A 49 year old woman was well until the fall of 1942, when she began to have blanching, cyanosis, coldness and puffiness in all the fingers and thumbs on exposure to cold or with nervous tension. The same signs were present in the toes in a milder form. These manifestations started shortly after a daughter had encephalitis in 1941. The hands had been unusually cold for some years prior to the onset of the other signs. During the winter of 1942-1943 she experienced cracking of the skin of the left index and right fourth fingers. Numbness and tingling of the fingers accompanied the attacks of vasospasm. The patient felt very tired and nervous and complained of flushes for the past six years. She had not been helped by being told by a physician that gangrene

of the hands might develop. She also had a history of paroxysmal tachycardia for the past twenty years. One ovary and the uterus had been removed for fibroids in 1938.

Physical examination when she was first seen in December, 1944, disclosed all the fingers to be puffed but not blanched or cyanotic. The veins on the dorsa of the hands were small but visible. All pulses were palpable at the wrists and oscillometric readings were low normal. When the vascular tone test was done, however, during the period of cooling the veins on the dorsa of the hands constricted and became invisible. During this period the hands became blanched, then ruborous and then rapidly cyanotic. The fingers became very puffy during this period. When heat was applied to the trunk, the veins on the hands gradually dilated and the fingers assumed a normal color. The fingers were less swollen but still had a puffed appearance. The rest of the physical examination revealed no definite abnormalities. The blood pressure was 128 systolic and 88 diastolic. The throat, neck, heart, lungs, abdomen and spine were normal. The basal metabolic rate was —12 per cent. Roentgenologic examination of the hands showed nothing abnormal.

This swelling of the fingers, together with blanching and cyanosis, was present in varying degree in 8 of the 10 patients with Raynaud's disease. In most of these patients the veins on the dorsa of the hands were invisible even while there was vasodilatation.

CASE 2.—*Raynaud's disease; arterial spasm.*

A 47 year old woman had begun to have dead white fingers on exposure to cold and with emotional tension three years previously. Cyanosis was usually intermingled with the pallor. On return to a warm environment the hands became red. There was no swelling. Numbness and tingling also occurred during the attack. Her hands and feet have been cold all of her life. A hysterectomy had been performed when the subject was 20 years old.

On examination, all pulses at the wrists and ankles were palpable. Oscillometric readings were on the low side of normal. The hands and feet were cold. A reactive hyperemia test disclosed no signs of organic digital arterial occlusion. Placing the left hand in ice water brought on blanching of the distal phalanges and slight blanching of the proximal phalanges. The fingers had no signs of puffiness. The ridges in the skin on the fingers were all plainly visible. The veins on the dorsa of the hands were prominent while there was vasodilatation and were definitely visible even when constricted.

It is interesting that this was the only patient of the 10 seen by us in whom arterial spasm alone appeared to be present. Venospasm as well as arterial spasm was present in all the others except the patient with so-called cold allergy, in whom venospasm occurred alone.

COMMENT

The confusion that exists in interpreting the series of events in patients with Raynaud's disease and with Raynaud's phenomenon has arisen, we believe, from failure to consider that the veins often partake in the pathologic spasm. It is of interest that Raynaud himself[8]

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8. Raynaud, A. G. M.: De l'asphyxie locale et de la gangrène symmétrique des extrémités, Paris, Rignoux, 1862.

described a type of digital spasm in which veins must have been involved. In observation II, he gave this description: "Madame X, 25 years old, . . . has been very subject for a long time to having dead fingers. These become in an instant the seat of coldness, pallor and absolute insensibility . . . The fingers presented a very peculiar conformation. They were extremely large and soft, the hands themselves appeared edematous and they formed a very striking contrast with the slender wrists and forearms."

It is well known that a variety of pathologic states are created as a result of venospasm. The severe edema that may occur in thrombophlebitis has been recognized as often being caused by the constriction of many veins in the extremity as the result of reflexes set up in the one segment of vein which is inflamed and in a state of irritability. It is also recognized that the venous congestion that occurs in thrombophlebitis initiates reflex arterial constriction. This appears to be a necessary reflex to prevent the continued swelling of the extremity which would occur if the arteries remained dilated. This useful reflex tends to prevent extreme edema when veins are obstructed or in spasm. It has also been shown that simply congesting the veins in one extremity causes widespread changes in tone of both arteries and veins in the contralateral as well as in the same extremity.

It is our impression that this reflex may be a basic factor in inducing the arterial spasm in some patients with Raynaud's disease. The appearance of cyanosis and puffiness at the beginning of an attack in some patients suggests that venospasm occurs first, and that then, with distention of venules and capillaries distal to the spastic veins, reflex arterial constriction is initiated to prevent the swelling and congestion that would occur if the arteries remained unconstricted or dilated. An anatomic factor that fits into this concept of what may be happening in some patients with Raynaud's disease is that the veins in the hands are more superficially placed and are the first to be exposed to a stimulus such as cold.

Venous reflexes play an important role in certain physiologic processes. One of the mechanisms in the regulation of the circulation when a person assumes the erect posture is initiated by incipient distention of the veins.[9] This stretch reflex has been found to act as a stimulus to the production of arterial constriction in the lower extremities while a person is in the upright position, to prevent the dumping of too much blood into the legs. The process of frequent turning in bed during sleep is a result of an irritative reflex set up in veins as blood accumulates in them when no muscular movement occurs. Finally,

9. Jackson, M. M.: Anticipatory Cardiac Acceleration During Sleep, Science **96**:564, 1942.

when there is sufficient venous distention a reflex is set in motion which makes a person turn and move the muscles which massage the blood out of the veins.[9]

Thus far, mention has been made only of an exaggerated constriction of veins and arteries to cold and emotional tension as an explanation of the clinical picture in Raynaud's disease and in Raynaud's phenomenon. However, one other factor must be considered, the possibility that in some of these patients the capacity for venous outflow is not as great as it should be in relation to the capacity for arterial inflow. It is possible that there may be an imbalance between arterial and venous flow. We have observed, as have many others, the great variation in the caliber of veins in the hands and arms in different persons. Many of the patients with Raynaud's disease have small veins. A disproportion in the caliber of arteries and veins may in itself largely explain the cyanosis and puffiness. This is confirmed by the fact that cyanosis persists after sympathectomy in patients with Raynaud's disease, and may even increase, as in a patient mentioned by Lewis.[2] In these patients blanching (due to spasm) has been alleviated by sympathectomy, but the remaining cyanosis is explained by this basic anatomic disproportion between arteries and veins. This is further confirmed by the fact that Fulton's patient (described by Lewis) had an increase in cyanosis in the early morning following a probable period of vasodilatation during sleep. One of our patients, on whom sympathectomy was performed chiefly because of severe pain, behaved in a similar manner. There was relief of the pain following sympathectomy, but she continued to have puffy, cyanotic fingers, although the fingers no longer blanched. We do not see how this can be explained on any other basis than of a disproportion in arterial and venous capacity, since sympathectomy was performed on both arteries and veins.

It has been suggested by Hunt[10] that true Raynaud's disease is rare and that most patients who are seen with vasospastic phenomena in the hands have Raynaud's phenomenon. Lewis[2] has suggested that the term "Raynaud's disease" should be dropped entirely. Still others have expressed differing views as to what should be called Raynaud's disease and what should be called Raynaud's phenomenon.

It is our feeling that if the connotation of severity attached to the term "Raynaud's disease" is removed both terms are useful. We have found that a tendency to an exaggerated constriction of digital vessels is not uncommon. We know that there is a tremendous range in vascular tone in the hands of normal persons. Failure to realize that there is also a wide range in abnormal digital constriction to cold

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10. Hunt, J. H.: Raynaud Phenomena: Critical Review, Quart. J. Med. **5**:399, 1936.

and emotional tension has given an undeservedly serious connotation to the diagnosis of Raynaud's disease. The great majority of these persons have only mild symptoms, which do not increase in severity. It is only those with the severest grades of digital vasoconstriction who require sympathectomy. Only 3 of 10 patients with Raynaud's disease had small necrotic lesions at the finger tips, and of these only 1 required bilateral upper thoracic sympathectomy. Sympathectomy is indicated only in the presence of severe symptoms and beginning necrosis. The others were all treated conservatively, with special emphasis on reassurance. In the milder forms of Raynaud's spasm, reassurance is sufficient, together with mild vasodilator therapy. Many of these patients are frightened by the diagnosis of Raynaud's disease. When it is explained to them that they have simply a mildly exaggerated vascular response to cold and to emotional tension, their dread of gangrene is usually allayed, and this in itself reduces the tendency to vasoconstriction. It must be remembered that the emotional stimulus is present constantly in these patients, whereas the stimulus of cold can be removed. Treatment directed toward reducing nervous tension is extremely necessary, and reassurance as to the nature of the condition is of paramount importance. Mufson[11] has emphasized the role of psychic factors in Raynaud's disease. His article points out that in some patients only the removal of the cause of severe nervous tension will prevent attacks. We have seen the first attack of dead whiteness in the fingers precipitated in several patients by a severe emotional shock, such as the death of a member of the family. We have been impressed by the presence of factors that maintain a high degree of nervous tension in practically all patients with Raynaud's disease.

The program of management also includes, of course, avoidance of exposure to severe cold, wearing of warmer clothing than that worn by the average person, taking of a warm tub bath daily in a warm bathroom, abstinence from tobacco and use of an adequate diet. We have also found thyroid of value, since even a slightly reduced basal metabolic rate will aggravate a tendency to peripheral vasoconstriction in response to cold. Estrogen therapy is useful when Raynaud's disease occurs during the menopause. Vasodilators such as mecholyl bromide we have found of only occasional benefit. We reserve sympathectomy for the occasional case of severe type, in which the disease is obviously progressing and digital necrosis is beginning to develop. We have never seen the loss of even part of a digit from Raynaud's disease. One must, of course, rule out thromboangiitis obliterans in the presence of digital gangrene.

11. Mufson, I.: The Mechanism and Treatment of Raynaud's Disease: A Psychosomatic Disturbance, Ann. Int. Med. **20**:228, 1944.

The term "Raynaud's phenomenon" should be reserved for digital vasospasm, secondary to other known pathologic conditions. Conditions in which secondary digital vascular spasm occurs include scleroderma, cervical rib, scalenus anticus syndrome, pneumatic hammer disease, arthritis, various neurologic diseases, pressure from a. crutch, causalgia and probably other diseases.

It should be noted that we have limited the terms "Raynaud's disease" and "Raynaud's phenomenon" to bilateral, symmetric digital involvement. Where vasospasm is present in one extremity it should be called simple vasospasm. There is usually a local explanation, either in the extremity or in the spine, for such unilateral vasoconstriction.

SUMMARY

Observation of 10 patients with Raynaud's disease and 4 patients with Raynaud's phenomenon has disclosed evidence that spasm of the veins as well as of the arteries is present in the majority of these patients. Arterial spasm alone cannot explain the clinical picture in most patients.

In some patients venospasm may predominate over arterial spasm. The clinical features in each patient will vary depending on which part of the vascular tree is predominantly involved in the abnormal vasoconstriction.

It is suggested that in some patients with Raynaud's disease the clinical picture is influenced by an anatomic disproportion in capacity between arterial and venous flow.

On the basis of clinical observations of these patients during the test for basal vascular tone, a classification has been made to clarify the terms "Raynaud's disease" and "Raynaud's phenomenon."

Raynaud's disease is not rare. The milder forms are fairly common and do not deserve the connotation of seriousness usually associated with the diagnosis. Reassurance is an important part of treatment.

In a patient with so-called cold allergy venospasm was found to develop on exposure to cold without development of arterial constriction, which explained the development of cyanosis and pronounced swelling without blanching.

PURPURIC MANIFESTATIONS OF HEATSTROKE

Studies of Prothrombin and Platelets in Twelve Cases

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THE appearance of purpuric manifestations in heatstroke has been recorded by several authors.[1] According to Wakefield and Hall,[2] Andnal gave the first accurate account of the major postmortem features in 1838—namely, petechiae, liquid blood and venous engorgement. In 1892 Osler[3] wrote: "The venous engorgement is extreme, particularly in the cerebrum. The blood is usually fluid; the lungs are intensely congested. Parenchymatous changes occur in the liver and spleen."

In a review of available literature concerning heatstroke we have not found an adequate explanation of this hemorrhagic phenomenon. However Wilson and Doan[4] reported decreases in prothrombin and platelets in patients subjected to artificially induced fever. They concluded that the decrease in prothrombin was secondary to hepatic damage and that the degree of thrombopenia depended on the extent of megakaryocytic damage.

The purpose of this report is to record the results of repeated determinations of prothrombin time and platelet counts on 12 patients critically ill with heatstroke and to point out evidence suggesting that an increase in capillary permeability occurs.

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1. (*a*) Gauss, H., and Meyer, K. A.: Heat Stroke: Report of One Hundred and Fifty-Eight Cases, Am. J. M. Sc. **154**:554, 1917. (*b*) Wilcocks, C.: Effects of Heat in Persia and Iraq, Trop. Dis. Bull. **41**:74 (Jan.) 1944. (*c*) Wilson, G.: The Cardiopathology of Heatstroke, J. A. M. A. **114**:557 (Feb. 17) 1940.

2. Wakefield, E. G., and Hall, W. W.: Heat Injuries, J. A. M. A. **89**:92 (July, 9) 1927.

3 Osler, W.: Principles and Practice of Medicine, New York, D. Appleton and Company, 1892, p. 1017.

4. Wilson, S. J., and Doan, C. A.: The Pathogenesis of Hemorrhage in Artificially Induced Fever, Ann. Int. Med. **13**:1214 (Jan.) 1940.

The Quick method [5] using undiluted plasma was the procedure employed in all determinations of prothrombin time. Simultaneous and identical tests were performed on normal plasma. Bacto-thromboplastin [6] was used in all tests and controls. Clot formation is obtained in twelve to fourteen seconds with this thromboplastin preparation and normal undiluted plasma. Clot formation occurred in most of our controls in fourteen seconds. Since all control tests were on normal undiluted plasma we recorded prothrombin time in seconds instead of in per cent of normal.

All platelet counts were made by the direct method of Rees and Ecker.[7] The normal count by this method is 200,000 to 500,000.

The hyperpyrexia was reduced by a routine method consisting of continuous water sponges, brisk massage of the trunk and extremities and directing electric fans on the patient.

TABLE 1.—*Laboratory and Clinical Observations*

Case number	1	2	3	4	5	6	7	8	9	10	11	12
				On	Admission							
Temperature	110	109	108	110	110	110	110	110	110	110	106	106
Unconsciousness	+	+	+	+	+	+	+	+	+	+	−	−
Dry skin	+	+	+	+	+	+	+	+	+	+	+	+
Blood pressure	130/60	136/90	132/84	125/70	136/90	130/80	90/60	100/60	120/90	?/?	?/?	132/80
Cyanosis	+	+	+	+	+	+	+	+	+	+	0	0
Petechiae	+	+	+	+	+	+	+	h+	+	m−	−	−
Prothrombin time (sec.)	14	20	14	?	16	17	30	16	16	15	14	17
Platelets (thousands)*	80	68	?	?	92	40	?	104	120	?	80	63
				Subsequently								
Incontinence	+	+	+	+	+	+	+	+	+	+	−	−
Convulsions	+	+	0	+	+	0	−	0	−	−	−	−
Decreased capillary tone	+	+	+	+	+	+	+	+	?	?	−	−
Vomiting	+	+	+	?	+	+	+	+	+	+	+	+
Rales and rhonchi	+	+	+	+	+	+	+	?	+	+	+	−
Petechiae	+	+	+	+	+	+	h+	h+	+	m+	−	−
Prothrombin time (sec.)†	38	35	30	108	20	20	30	20	?	?	17	17
Platelets †	40	68	85	70	31	35	?	?	?	?	50	30
Bleeding time (min.)†	12	4¼	3	10	6	9	?	?	?	?	3	3
Icterus index †	47	9	31	+?	15	?	?	?	?	?	9	?
Died (hours survived)	..	..	..	72	288	..	6	9½	5½	5½		

* Maximum deviation from normal for the twenty-four hour period.
† Maximum deviation from normal during the illness.
The letter h indicates hematemesis. The letter m indicates melena.

Laboratory and clinical observations are summarized in table 1, and a brief clinical report of the facts germane to the hemorrhagic phenomena is given for each case.

REPORT OF CASES

CASE 1.—A white man aged 31 was admitted to the hospital at 5:30 p. m. on Sept. 6, 1944, with a temperature of 110 F. He was deeply cyanotic, uncon-

5. Quick, A. J.: Nature of Bleeding in Jaundice, J. A. M. A. **110**:1658 (May 14) 1938; Prothrombin in Preserved Blood, ibid. **114**:1342 (April 6) 1940.

6. A product of Difco Laboratories, Detroit, Mich.

7. Kracke, R. R., and Parker, F. P.: A Textbook of Clinical Pathology, Baltimore, Williams & Wilkins Company, 1940, p. 130.

scious and restless and was having recurrent generalized convulsions. The blood pressure was 130 systolic and 60 diastolic. The skin was hot and dry, and many petechiae were noted. Rales and wheezes were heard throughout both lungs. All deep reflexes were absent. The temperature was reduced to 101 F. within one hour. His blood pressure fell to 80 systolic and 60 diastolic soon after his admission but was restored to its previous level after an infusion of 500 cc. of plasma. The prothrombin time was fourteen seconds. The platelet count was 80,000.

On September 7, consciousness had returned and the patient's general appearance was good. The lungs were much clearer. However, there was a noticeable increase in the number of petechiae. The prothrombin time was twenty-three seconds, and the platelet count was 28,000.

On September 8, he continued to improve. The prothrombin time was thirty-eight seconds, platelet count 72,000, bleeding time ten minutes and forty seconds and icterus index 25.

On September 9, the lungs were clear. The prothrombin time was thirty-six seconds, platelet count 66,000, bleeding time twelve minutes and icterus index 47.

On September 10, he appeared well. The prothrombin time was nineteen seconds, platelet count 52,000 and bleeding time twelve minutes.

On September 11, the prothrombin time was eighteen seconds, platelet count 146,000, bleeding time six minutes and icterus index 57.

On September 13, the prothrombin time was fourteen seconds, platelet count 130,000, bleeding time eight minutes and icterus index 47.

On September 15, the platelet count was 120,000 and the bleeding time five minutes and fifty seconds.

On September 17, the platelet count was 298,000, bleeding time four minutes and icterus index 17.

The convalescence was uneventful.

CASE 2.—A white man aged 23 was admitted to the hospital July 19, 1944, with a temperature of 110 F. He was cyanotic, unconscious, vomiting and incontinent of urine and feces. The blood pressure was 136 systolic and 90 diastolic. The skin was dry, and petechiae were present on the abdomen and thorax. Large conjunctival hemorrhages were present in both eyes. All deep reflexes were absent. The temperature was reduced to 103 F. in less than three hours. The prothrombin time was fifteen seconds on his admission and a few hours later was twenty seconds. The platelet count was 68,000.

On July 20, he remained unconscious and critically ill. The prothrombin time in the morning was nineteen seconds, and when the determination was repeated in the afternoon it was twenty-eight seconds. The icterus index was 19, platelet count 68,000 and bleeding time four minutes and fifteen seconds.

On July 21, he regained consciousness but remained stuporous and confused throughout the day. The prothrombin time was thirty-five seconds.

On July 22, he was more alert but was unable to find the correct words to express himself. The prothrombin time was eighteen seconds.

On July 23, he seemed much improved. It was recorded that he was ataxic. The icterus index was 9, and the oral hippuric acid test showed 68 per cent normal excretion.

On July 24, the prothrombin time was fourteen seconds, and the platelet count was 200,000.

His recovery was slow and uneventful except for the ataxia, which persisted in some degree for three weeks.

CASE 3.—A white man 36 years of age was admitted to the hospital July 29, 1944, with a temperature of 108 F. He was cyanotic, unconscious and incontinent. Many petechial hemorrhages were noted in the conjunctivas and on the abdomen. chest and extremities. The deep reflexes were greatly diminished. Rhonchi and rales were heard throughout both pulmonary fields. His temperature was reduced to 101 F. in four hours, and consciousness returned in six hours. The prothrombin time was fourteen seconds on his admission; a few hours later it was nineteen seconds.

On July 30, the maximum temperature was 101 F. The lungs were clear. The prothrombin time was twenty-seven seconds in the morning and thirty seconds in the afternoon.

On July 31, the maximum temperature was 101.4 F. The prothrombin time was twenty-three seconds, icterus index 25, bleeding time three minutes and platelet count 85,000.

On August 1, he no longer appeared acutely ill. The maximum temperature was 100.6 F. The prothrombin time was nineteen seconds, platelet count 85,000 and bleeding time normal.

On August 2, the prothrombin time was fifteen seconds, platelet count 132,000 and bleeding time normal. The icterus index was 31.

The remaining course was uneventful; the icterus index was 17 on August 5 and 10 on August 8. The platelet count was 268,000 on August 6.

CASE 4.—A white youth 18 years of age was admitted to the hospital at 7 p. m. on May 19, 1943, with a temperature of 110 F. He was unconscious; the skin was dry, and petechiae were noted. The temperature was reduced to 101 F. in two hours.

On May 20 showers of petechiae appeared on the extremities and trunk. The prothrombin time was forty-nine seconds. Five milligrams of menadione (vitamin K) was given parenterally, and the dose was repeated every six hours. The prothrombin time was one hundred and eight seconds, bleeding time ten minutes and platelet count 90,000 six hours after the first dose of the vitamin K preparation.

On May 21, the prothrombin time was seventy-two seconds, and the platelet count was 70,000. He was conscious and cooperative and answered questions readily. The improvement lasted only a few hours. There was an increase in temperature as well as in respiration and pulse rate. Evidence of an area of consolidation in the right lung was detected and confirmed by roentgenogram. A previous roentgenogram had been normal. A transfusion of 500 cc. of whole blood was given and was repeated during the night.

On May 22, the patient died at 6 a. m.

The pathologic diagnoses included mild diffuse icterus, petechiae of the skin, mild diffuse hemorrhage in the myocardium, severe multiple interstitial pulmonary hemorrhages, multiple petechial hemorrhages in the stomach and intestines, multiple small hemorrhages in the pancreas and spleen, multiple diffuse perivascular hemorrhages in the brain, moderately severe fatty degeneration of the liver and pneumonia with consolidation in the upper lobe of the right lung and a separate consolidation in the middle portion of the lower lobe of the right lung.

CASE 5.—An obese white man, 25 years of age, was admitted to the hospital Sept. 6, 1944, with a temperature of 110 F. He was unconscious, cyanotic, vomiting and incontinent. The blood pressure was 130 systolic and 90 diastolic. The skin was dry, and petechiae were present on the abdomen, chest and arms.

Rales and rhonchi were heard throughout both lungs. The deep reflexes were absent. His temperature was reduced to 100.4 F. in three hours. He had several generalized convulsive seizures during the first few hours. A few minutes after his admission the prothrombin time was sixteen seconds, and the platelet count was 108,000. A few hours later the platelet count was 92,000 and the prothrombin time twenty seconds.

On September 7, he remained unconscious and cyanotic. The blood pressure was 92 systolic and 50 diastolic. Hemorrhages in the eyes and skin were more prominent. The prothrombin time was eighteen seconds, platelet count 44,000 and bleeding time four minutes and fifty seconds.

On September 8, his unconsciousness continued. A transfusion of 400 cc. of whole blood was given. The platelet count was 31,000 and the bleeding time was three minutes. The prothrombin time was fourteen seconds and remained normal until the day of his death.

On September 9, he remained critically ill. Rales and rhonchi were present throughout both pulmonary fields. The platelet count was 78,000.

On September 10, a transfusion of 500 cc. of whole blood was given. The platelet count was 66,000, and the bleeding time was six minutes.

On September 11, he regained consciousness but was unable to speak. The bleeding time was six minutes and ten seconds, platelet count 168,000 and icterus index 15.

On September 12, 13, 14 and 15, there was slight improvement. Daily platelet counts were 94,000, 130,000, 178,000 and 140,000, respectively. The bleeding time varied from six to eight minutes. Once every twenty-four hours his temperature would rise to 107 or 108 F. but was promptly controlled by cool water sponges.

On September 16, his temperature did not exceed 104 F., and he seemed to be doing well.

On September 17, an acute pulmonary edema developed late in the afternoon, and the patient died at 6:30 p. m. The prothrombin time was sixteen seconds, and the platelet count was 260,000, about eight hours before death.

The pathologic diagnoses were: petechiae in the skin of the trunk, severe multiple pulmonary hemorrhages, severe bilateral pulmonary edema, acute early bronchopneumonia, severe acute purulent bronchitis, small mucosal hemorrhages of the large and small intestines, multiple small petechial hemorrhages of the subarachnoid spaces and necrosis of the liver.

In this case the prothrombin index was normal except for a slight deficiency during the first forty-eight hours and on the day of death. This is of particular interest because the most outstanding pathologic change was a severe central necrosis of the liver in which approximately 60 per cent of the parenchyma was destroyed. Conclusive evidence of megalokaryocytic damage could not be demonstrated in postmortem smears of bone marrow.

CASE 6.—A white man aged 26 was admitted to the hospital Sept. 5, 1944, with a temperature of 110 F. He was unconscious, cyanotic, vomiting and incontinent. The blood pressure was 130 systolic and 80 diastolic. The skin was dry. Petechiae were present on the trunk, and bilateral conjunctival hemorrhages were observed. Rales and rhonchi were heard throughout both lungs. Deep reflexes were present but extremely weak.

The blood pressure dropped to 80 systolic and 50 diastolic, but the systolic pressure rose to 106 after an infusion of 500 cc. of plasma.

The prothrombin time was seventeen seconds, and the platelet count was 40,000 a few minutes after his admission.

On September 6, rales and respiratory wheezes could be heard throughout both lungs. Late in the morning consciousness returned. The prothrombin time was twenty seconds; the platelet count was 80,000 in the morning and 40,000 late in the afternoon.

On September 7, no additional petechiae were noted. Deep reflexes had improved. Prothrombin time was twenty seconds, platelet count 35,000 and bleeding time four minutes and thirty-five seconds.

On September 8, he was greatly improved. The prothrombin time was normal, platelet count 50,000 and bleeding time six minutes. A hippuric acid test (oral) showed 37 per cent normal excretion.

On September 9, the platelet count was 72,000, and the bleeding time was four minutes and thirty seconds.

On September 10, he appeared well. The prothrombin time was eighteen seconds, platelet count 82,000 and bleeding time nine minutes.

On September 11, the prothrombin time was normal, platelet count 132,000 and bleeding time six minutes.

His recovery was slow but without special event. The platelet count had increased to 238,000 by September 13.

CASE 7.—A white man 27 years of age was admitted to the hospital June 17, 1944, with a temperature of 110 F. He was unconscious, cyanotic and incontinent. The blood pressure was 90 systolic and 60 diastolic. All deep reflexes were absent. Petechiae were noted on the chest and about the ankles. He vomited a small amount of blood.

He grew progressively worse and died six hours after his admission. The prothrombin time soon after his admission was thirty seconds.

The pathologic diagnoses were: petechial hemorrhages in the skin, moderate subepicardial and subendocardial hemorrhage and severe multiple bilateral pulmonary hemorrhages. (The right lung weighed 760 Gm. and the left 1,100 Gm.) Pulmonary hemorrhages were a contributory cause of death.

CASE 8.—A white man aged 25 was admitted to the hospital Sept. 5, 1944, with a temperature of 110 F. The blood pressure was 100 systolic and 60 diastolic. He was cyanotic, unconscious and incontinent. All deep reflexes were absent.

Four hours after admission he vomited a large amount of blood. Purpuric spots were noted on the trunk. About nine hours after his admission the systolic blood pressure fell to 70; the cyanosis became intense, and the patient died.

The prothrombin time was sixteen seconds on his admission; eight hours later it was twenty seconds. The platelet count was 104,000.

The pathologic diagnoses were: petechial hemorrhages in the skin, subendocardial hemorrhage on the left surface of the intraventricular septum, massive pulmonary hemorrhage of the right lung (weight 1,640 Gm.) and a smaller amount in the left lung (weight 500 Gm.) and hemorrhage of the gastric mucosa. ·

CASE 9.—A white man 37 years of age was admitted to the hospital July 18, 1944, with a temperature of 110 F. He was unconscious and deeply cyanotic. The blood pressure was 120 systolic and 90 diastolic. The pulse was rapid and of poor volume. He became progressively worse and died six hours after his

admission. The prothrombin time was sixteen seconds. The platelets numbered 120,000 soon after his admission.

The pathologic diagnoses were: petechial hemorrhages in the skin, subepicardium, gastric mucosa, small and large intestines, pancreas and subendocardium of left intraventricular surface; massive bilateral pulmonary hemorrhage; moderate pulmonary edema (the right lung weighing 1,360 Gm. and the left 1,000 Gm.), and mild cerebral edema.

CASE 10.—A white man 21 years of age was admitted to the hospital July 18, 1944, with a temperature of 110 F. He was unconscious, cyanotic and incontinent and was vomiting. The pulse was rapid and of poor volume. The blood pressure reading was unobtainable. Rhonchi and rales were heard throughout both lungs. He was given a 500 cc. infusion of plasma.

Three hours after his admission the systolic blood pressure was 40 mm. of mercury. A few minutes after his admission the prothrombin time was normal. Five hours after admission he passed a large bloody stool and died thirty minutes later.

The pathologic diagnoses were: severe generalized dehydration, severe generalized passive congestion, multiple mild pulmonary atelectasis (weight of right lung 800 Gm. and of left lung 600 Gm.), mild subepicardial hemorrhages, superficial subendocardial hemorrhage of the left side of the intraventricular septum and severe gastrointestinal hemorrhage.

CASE 11.—A white youth aged 18 was admitted to the hospital Aug. 30, 1944. His temperature was 106 F. He was conscious but confused. The skin was dry, but no petechiae were noted. The lungs were clear; deep reflexes were present and equal. The temperature was reduced to 100.6 F. in three hours. His recovery was rapid and uneventful. The prothrombin time on his admission was fourteen seconds and a few hours later seventeen seconds. The platelets numbered 302,000 on his admission and a few hours later 80,000.

On August 31, the platelet count was 88,000. The prothrombin time and bleeding time were normal.

On September 1, the platelet count was 50,000; the prothrombin time and bleeding time remained normal. The icterus index was 9.

On September 2, the platelet count was 108,000, and the icterus index was 9. The oral hippuric acid test showed 44 per cent normal excretion.

CASE 12.—A white man aged 35 was admitted to the hospital Sept. 6, 1944, with a temperature of 106.4 F. He appeared weak and apprehensive, but he was mentally alert. The blood pressure was 132 systolic and 84 diastolic. The skin was dry, but no petechiae were noted. The deep reflexes were present and equal. The temperature was reduced to 101 F. in one hour. The initial prothrombin time was seventeen seconds; other repeated determinations were normal. The platelet count on his admission was 63,000 and a few hours later 30,000. The second day the platelet count was 130,000, the third day 135,000 and the fourth day 158,000. The bleeding time did not exceed three minutes. His recovery was rapid and uneventful.

COMMENT

Decrease of capillary tone or elasticity could be demonstrated in the severely ill patients by inflating a blood pressure cuff to a point midway between the systolic and the diastolic pressure. Distal to the constriction a striking mottled cyanosis appeared and persisted from three to five

minutes after the constriction was released. This could be demonstrated for several days in patients who survived, disappearing about the time the patient resumed sweating. It may be that the physiologic capillary, dilation that occurs on exposure to high environmental temperature reaches a pathologic state, permitting red cells and plasma to extravasate. Such an increase in capillary permeability would explain the presence of petechiae in cases 8 and 9 on the patients' admission, when the pro- . thrombin times were sixteen seconds and the platelet counts were more than 100,000. This slowly disappearing mottled cyanosis distal to the constriction could not be demonstrated in the 2 mildly ill patients (cases

TABLE 2.—*Observations at Necropsy*

Case number	4	5	7	8	9	10	A*	B*	C*	D*	Total Cases
Bronchopneumonia	3+	2+	1+	...	...	...	...	...	...	...	3
Pulmonary edema	...	4+	...	...	...	...	...	...	...	2+	2
Atelectasis	...	2+	...	...	...	3+	...	...	1+	...	3
Necrosis of liver	3+	3+	...	...	...	...	...	...	...	...	2
Hemorrhage:											
Pulmonary	3+	4+	3+	3+	3+	2+	2+	2+	3+	2+	10
Skin	4+	2+	3+	4+	3+	...	...	2+	1+	3+	8
G. I. mucosa	3+	2+	...	2+	3+	2+	...	...	2+	2+	7
Subepicardial	...	2+	3+	...	2+	2+	...	1+	...	3+	6
Myocardial	...	...	...	...	...	...	1+	...	...	...	1
I. V. septum †	...	...	3+	4+	3+	2+	...	4+	3+	3+	7
Subarachnoid	2+	2+	...	...	...	...	3+	2+	...	...	4
Brain (perivascular)	2+	...	1+	...	...	2+	...	...	...	...	3
Pancreatic	2+	...	...	3+	...	...	...	...	...	...	2
Diaphragmatic	...	...	...	...	...	...	...	2+	...	...	1
Mediastinal	2+	...	...	...	...	...	...	...	...	...	1
Splenic	2+	...	...	...	...	...	...	...	...	...	1
Hepatic	...	...	...	...	...	...	...	...	2+	...	1
Coalescence of RBC in cerebral capillaries	...	...	...	3+	...	...	2+	...	2+	...	3
Survival in hours	72	288	6	9.5	5.5	5.5	1	11.5	3	0.3	

* Protocols available but not included in this study.
† Subendothelial hemorrhage in intraventricular septum.

11 and 12), whose temperatures did not exceed 106.4 F., indicating that capillary damage was not so profound. This would explain why petechiae did not appear in these 2 mildly ill patients when the platelets numbered 30,000 and 50,000. Therefore, it seems plausible to postulate that, in addition to a decrease in prothrombin time and/or platelet count, a third factor, namely, capillary damage, contributes to the pathogenesis of the hemorrhagic manifestations of heat stroke.

Table 2 summarizes the pathologic observations. The location and severity of the purpuric manifestations are indicated. Four protocols in addition to the reports of cases presented here were available for review and have been included in this table.

The significance of this hemorrhagic phenomenon is not easily evaluated. The actual volume of blood lost was not sufficient to cause death, and the patient in case 3 was the only one in whom the amount lost was a valid contribution to the cause of death. The mechanical effect of the pulmonary hemorrhage was a serious complication in cases 4, 5, 7, 8 and 9. Wilson [1e] reported subendocardial hemorrhage in 1 case of sunstroke and in 3 cases of uncontrollable hyperpyrexia resulting from artificial fever therapy. He concluded: "The most striking and probably the actual fatal mechanism is a rather extensive hemorrhage under the endocardium of the left ventricle especially in the septal wall in the region of the bundle of His." We were not aware of this report at the time we observed these patients, and special studies to determine damage to the conduction system were not made. However, subendothelial hemorrhage in the intraventricular septum was recorded in 7 of the 10 available protocols reviewed and included in table 2. The survival time of the 7 patients varied from a few minutes to eleven hours. Electrocardiographic studies were impractical in examination of these patients owing to spasticity, muscular fibrillation, convulsions or purposeless movement. Conduction defects were not demonstrated electrocardiographically in patients who survived. It is unfortunate that we were not able to determine the number of platelets and the prothrombin activity just prior to death in the 4 patients who survived less than ten hours.

The extensive hepatic damage found at necropsy in cases 4 and 5 plus the abnormal results of the hippuric acid tests in the 3 cases in which they were performed are evidence that the decrease in prothrombin is due to hepatic damage. The elevated icterus indexes also suggest hepatic damage. However, the icterus may have been due in part to absorption of extravasated blood. Therefore, therapy should be directed to the prevention of damage to the liver—namely, intravenous administration of dextrose, vitamins, choline chloride and liberal amounts of protein and carbohydrates with a minimal amount of fat.

Smears of bone marrow obtained at necropsy and, in 1 case, shortly before death did not reveal unequivocal evidence of megalokaryocytic damage.

To become enthusiastic about therapeutic correction of the prothrombin and/or platelet deficiency, one would have to disregard three very important facts: 1. Heatstroke is not infrequently fatal in a few minutes or a few hours. 2. The quantity of blood lost is not the primary cause of death, and the part played by extravasation of plasma through the capillaries is an unknown quantity. 3. Hemorrhage in the lungs, myo-

cardium and elsewhere that might be of importance owing to the mechanical effect may occur too rapidly for therapy to be of value.

Dramatic results were not obtained by giving menadione parenterally in doses not exceeding 15 mg. for each twenty-four hour period. The number of cases studied and the amount of menadione given were too small to justify clinical conclusions. Since a deficiency of prothrombin is usually present a few hours after the onset of heatstroke, it would be wise to try large doses of menadione, 50 to 60 mg., parenterally when the patient is first seen. Such large doses have been successful in treatment of the untoward effects of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]).

The occurrence of thrombopenia and prothrombin deficiency dictates that early and repeated transfusions of whole blood might be of benefit. Early transfusions were not given in any of the cases herein reported.

Peripheral circulatory failure is not a cause of heatstroke, as evidenced by the fact that the systolic pressure was 130 or more on admission in 6 of our patients. This slight increase in systolic pressure plus the evidence of loss of capillary tone previously referred to suggests that the pooling of blood in dilated vessels may become sufficient to produce circulatory failure. Two patients (cases 6 and 1) did show decided drops in blood pressure soon after their admission, and definite improvement followed infusions of 500 cc. of plasma.

CONCLUSIONS

The hemorrhagic phenomena associated with heatstroke are due to an increase in capillary porosity and a decrease in prothrombin and/or platelets.

The resulting prothrombin deficiency is secondary to hepatic damage.

Large amounts of menadione administered parenterally, early transfusions of whole blood and a regimen to prevent or retard hepatic damage might be of some value in treatment of patients who survive the first few hours.

CHRONIC COR PULMONALE

Sixty Cases Studied at Necropsy

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COR PULMONALE is usually classified into the acute, subacute and chronic ,types. Acute cor pulmonale is generally caused by massive pulmonary emboli. If over 60 per cent of the vascular bed is occluded in this form, death will result almost immediately. The subacute form, the least frequent of the three, has been accurately described by Greenspan.[1] Secondary endolymphatic carcinomatosis of the lungs is the commonest cause of subacute cor pulmonale. In this condition the metastatic carcinoma diffusely infiltrates the perivascular lymphatics and then secondarily involves the pulmonary arterioles. This involvement interferes with the flow of blood through the pulmonary circuit and results in an increased burden on the right ventricle with eventual failure. The primary site for this type of secondary carcinomatous involvement of the lung is most often in the stomach, but in our experience carcinoma arising in the prostate, liver, kidney, breast or bronchus has also given rise to metastases with similar distribution. Brill and Robertson[2] reported that involvement of the smaller vessels by pulmonary emboli may also result in subacute failure of the right ventricle. Yater and Hansmann[3] have described 2 patients with sickle cell anemia with secondary pulmonary thrombosis in whom subacute cor pulmonale developed. Chronic cor pulmonale, the type with which this report is mainly concerned, results from a much greater variety of anatomic changes. These changes may arise primarily in the bony structures of the chest, in the pulmonary vascular tree or in the lung parenchyma. Those arising as a result of changes in the lung constitute the largest and most important group.

1. Greenspan, E. B.: Carcinomatous Endarteritis of Pulmonary Vessels Resulting in Failure of Right Ventricle, Arch. Int. Med. 54:625-644 (Oct.) 1934.

2. Brill, I. C., and Robertson, T. D.: Subacute Cor Pulmonale, Arch. Int. Med. 60:1043-1057 (Dec.) 1937.

3. Yater, W. M., and Hansmann, G. H.: Sickle Cell Anemia: New Cause of Cor Pulmonale; Report of Two Cases with Numerous Disseminated Occlusions. of Small Pulmonary Arteries, Am. J. M. Sc. 191:474-484 (April) 1936.

CLASSIFICATION

The following classification based on etiology has the additional advantage of grouping the cases according to the clinical behavior of the disease. This classification is not meant to be all-inclusive.

   I. Anatomic alterations of the thoracic cage
      A. Kyphoscoliosis
      B. Thoracoplasty
  II. Anatomic alterations of the pulmonary vascular system
      A. Main pulmonary arteries
         1. Intrinsic disease of the large pulmonary arteries, such as gummatous or cicatricial pulmonary arteritis (Warthin [4] and Cheney [5])
         2. Pressure on the large pulmonary vessels, such as aneurysm arising from the base of the aorta (Eichler [6] and Delp and Maxwell [7])
      B. Pulmonary arterioles
         1. Primary pulmonary arteriosclerosis; endarteritis obliterans (Ayerza's disease)
         2. Schistosomiasis of pulmonary vessels (Clark and Graef [8] and Shaw and Ghareeb [9])
 III. Anatomic alterations of the pulmonary parenchyma
      A. Primary pulmonary emphysema with or without fibrosis
      B. Primary pulmonary disease with secondary emphysema and fibrosis
         1. Pulmonary tuberculosis
         2. Pneumoconiosis
            a. Chronic silicosis
            b. Anthracosis (Ketterer [10] and Helpern [11])
         3. Bronchiectasis
         4. Bronchial asthma
         5. Acute interstitial fibrosis (Hamman and Rich [12])
         6. Multiple cysts of the lung (Willius [13])

4. Warthin, A. S.: Syphilis of the Pulmonary Artery, Am. J. Syph. **1**:693 (Oct.) 1917.

5. Cheney, G.: Ayerza's Disease: Report of Two Cases, Am. J. M. Sc. **174**:34-45 (July) 1927.

6. Eichler, B.: Personal communication to the authors; to be published.

7. Delp, M. H., and Maxwell, R.: Aneurysm of Aorta with Rupture into Pulmonary Artery, J. A. M. A. **10**:1647-1649 (May 14) 1938.

8. Clark, E., and Graef, I.: Chronic Pulmonary Arteritis in Schistosomiasis Mansoni Associated with Right Ventricular Hypertrophy: Report of a Case, Am. J. Path. **11**:693-706 (July) 1935.

9. Shaw, A. F. B., and Ghareeb, A. A.: The Pathogenesis of Pulmonary Schistosomiasis in Egypt with Special Reference to Ayerza's Disease, J. Path. & Bact. **46**:401-424 (May) 1938.

10. Ketterer, C. H.: Anthracosis and Chronic Pulmonary Heart Disease (Cor Pulmonale), M. Bull. Vet. Admin. **18**:98-100 (July) 1941.

11. Helpern, M.: Personal communication to the authors.

12. Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of Lungs, Bull. Johns Hopkins Hosp. **74**:177-212 (March) 1944.

13. Willius, F. A.: Cardiac Hypertrophy and Failure Secondary to Diffuse Bilateral Congenital Cystic Disease of Lungs, Proc. Staff Meet., Mayo Clin. **12**:572-575 (Sept. 8) 1937.

The term "emphysema" as used in this report refers to chronic obstructive emphysema that sometimes goes under the pseudonyms of "hypertrophic emphysema," "large lung emphysema" or "chronic vesicular emphysema." In this condition the lung is in a chronic state of hyperinflation resulting presumably from a diffuse incomplete obstruction of the finer bronchial air passages. On the other hand, it is thought that senile emphysema plays no part whatsoever in the development of cor pulmonale.

SELECTION OF CASE MATERIAL

Cor pulmonale is often a complicating factor of other forms of heart disease, particularly rheumatic heart disease, and occurs most frequently at the age when other forms of heart disease, such as arteriosclerotic and hypertensive forms, are prevalent. In order to present an unequivocal picture of this condition, we have eliminated from our series any case in which the possibility of another significant cardiac factor existed. The cases were selected first on the basis of their anatomic features, and only then was any recourse made to the clinical record. Sixty consecutive cases of cor pulmonale studied at necropsy were selected in which there were no significant evidences either clinical or anatomic, present or preexistent, of hypertension, valvular heart disease, congenital lesions, syphilitic cardiovascular disease or coronary atherosclerosis.

Most of the patients fell into the age group in which coronary atherosclerosis and hypertension are common occurrences. It was, therefore, possible to eliminate only those characterized by moderate to severe coronary arterial changes. Only those cases were selected as examples of cor pulmonale in which the walls of the right ventricle averaged over 5 mm. in thickness and in which the walls of the right ventricle were hypertrophied to a greater degree than those of the left ventricle. Consequently a number of cases of cor pulmonale occurring in pulmonary tuberculosis, in which the heart as a whole may be considerably reduced in size, may have been overlooked.

INCIDENCE AND ETIOLOGY

The fact that these cases are selected renders valueless an attempt to draw any significant conclusion from this series as to the frequency and incidence of this condition. However, in a report by Scott and Garvin [14] there were 50 cases of cor pulmonale described in a series of 6,548 necropsies. Of these 6,548 necropsies, 890 involved cases of cardiac disease. Cor pulmonale, therefore, formed 6.3 per cent of all cases of cardiac disease studied by them at necropsy.

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14. Scott, R. W., and Garvin, C. F.: Cor Pulmonale: Observations in Fifty Autopsy Cases, Am. Heart J. **22**:56-63 (July) 1941.

The types and the incidence of the etiologic factors responsible for the development of cor pulmonale in their cases are listed in table 1. In our series there was also a wide variety of etiologic factors (table 2). A cursory comparison will reveal that our observations are in essential agreement with those reported by Scott and Garvin.[14]

TABLE 1.—*Etiologic Factors (Scott and Garvin [14])*

Underlying Pulmonary Conditions	Number of Cases
Emphysema	32
Emphysema and silicosis	7
Emphysema and tuberculosis	5
Emphysema and silicotuberculosis	2
Silicosis	1
Fibrosis	1

TABLE 2.—*Etiologic Factors (Spain and Handler)*

Underlying Pulmonary Conditions	Number of Cases
Emphysema	40
Bronchiectasis	6
Bronchial asthma	6
Silicotuberculosis	3
Pulmonary tuberculosis	2
Kyphoscoliosis	1
Pulmonary arteriolarsclerosis	1
Organized pulmonary thrombi	1

Although not included in this series, there have been observed at Bellevue Hospital such conditions as partial occlusion of the pulmonary artery by an aortic aneurysm, schistosomiasis and anthracosis as causes of cor pulmonale.

AGE, SEX, RACE AND OCCUPATION

Of the 60 patients, 56 were men and 4 were women; 56 were white; 3 were Negroes, and 1 was Chinese. The peak age incidence was between

TABLE 3.—*Distribution by Age*

Age	All Patients	Patients with Emphysema
30 to 40	4	1
41 to 45	3	1
46 to 50	4	2
51 to 55	14	5
56 to 60	12	8
61 to 65	11	10
66 to 70	8	8
71 and over	4	4

50 and 65. For those patients in whom emphysema alone was the apparent etiologic agent, the peak age incidence was definitely higher than for the others (table 3).

Since in both this series and Scott and Garvin's series the number of women was so low, it became of special interest to evaluate the underlying etiologic factors in the conditions of the women. It was found that of the 4 women, in addition to emphysema, 2 had bronchial asthma and 1 had bronchiectasis, while only 1 had chronic emphysema unassociated with other obvious pulmonary disease.

The cause of cor pulmonale in Negroes was also found to follow the same etiologic pattern as in women in that primarily emphysema itself was not the sole underlying factor. Study of the Negroes revealed that emphysema was most likely secondary to other obvious anatomic changes: For example, 1 patient had pulmonary tuberculosis; 1 had bronchial asthma, and in another there were organized and recanalized pulmonary thrombi. This same general pattern was also noted in those patients under the age of 40, among whom, for example, 1 patient had asthma and 2 had bronchiectasis, while only 1 had chronic idiopathic emphysema.

A review of the occupations engaged in by these patients indicated that the majority were employed in hard labor, while only a few performed light or sedentary work. Because Bellevue Hospital serves primarily the low income group, it is not possible to draw any definite conclusions. It is our impression, however, that cor pulmonale is seen more commonly in those engaged in hard laboring occupations. This seems to be particularly true of those patients in whom emphysema alone is the sole underlying pulmonary factor.

Similarly, no definite conclusions can be drawn from the nationality of these patients. While many nationalities were represented, the majority came from the Slavic countries. This, again, is in accord with the findings of Scott and Garvin,[14] who reported that 68 per cent of their patients came from southeastern Europe.

PATHOGENESIS IN THORACIC DEFORMITIES

The 1 patient with kyphoscoliosis in this series was a 55 year old white man with a history of deformity of the chest since childhood. He had complained of a cough productive of mucoid sputum for many years, but it was only several months before his admission to the hospital that he noticed any dyspnea or edema of the ankles. He was admitted to the hospital in a state of congestive heart failure and within a few weeks died. At postmortem examination the myocardium of the right ventricle was seen to be extremely hypertrophied. There was pronounced chronic passive congestion of all the viscera. There was an extreme kyphoscoliosis with the convexity to the right. Emphysema was the only significant abnormal feature in the lungs.

Hertzog and Manz [15] collected 126 cases of heart disease associated with kyphoscoliosis reported in the literature. In the majority of these, the heart was displaced upward and to the opposite side of the scoliosis. The possibility theoretically exists, therefore, that larger pulmonary vessels are kinked by the displacement of the mediastinal structures. It is significant to point out that the constant associated feature in all these cases was the far advanced emphysema of the lung, so that actually it is probable that this is one of the prime factors in the production of the pulmonary hypertension.

Chapman, Dill and Graybiel [16] reported that the average duration of life from the onset of deformity in this type of patient is thirty years. They also noted that the tendency to the development of hypertrophy of the right ventricle was much greater in those patients in whom the scoliosis was to the right. Although constant dyspnea is the most frequent symptom present in this condition, in the case reported by us the dyspnea was an extremely late manifestation. Kyphoscoliosis is responsible for only a small proportion of the cases of cor pulmonale. It was present only once in the 60 cases reported in this series, was not present at all in Scott and Garvin's series [14] and was listed only once in the 38 cases reported by Hallock and Rigler.[17]

Another deformity of the chest which may be associated with cor pulmonale is a long-standing thoracoplasty. Through the courtesy of the medical examiner, we have had the opportunity to observe such a case. The patient was a man 45 years of age, who had had a complete thoracoplasty performed on the right side nine years previously for pulmonary tuberculosis. Detailed clinical studies are not available. However, he did not have any obvious signs of heart failure. The heart weighed 500 Gm. and the myocardium of the right ventricle was over 1 cm. in thickness. The pulmonary arteries and arterioles revealed advanced sclerotic changes. Considerable emphysema was present on the noncollapsed side. Whether the pulmonary hypertension resulted from the deformity of the chest or from the fibrosis and emphysema associated with the tuberculosis could not be determined. Undoubtedly, the question of whether or not long-standing thoracoplasty may result in a strain on the right side of the heart is a subject which deserves further study.

15. Hertzog, A. J., and Manz, W. R.: Right-Sided Hypertrophy (Cor Pulmonale) Caused by Chest Deformity, Am. Heart J. **25**:399-403 (March) 1943.

16. Chapman, E. M.; Dill, D. B., and Graybiel, A.: The Decrease in Functional Capacity of the Lungs and Heart Resulting from Deformities of the Chest: Pulmonocardiac Failure, Medicine **18**:167-202 (May) 1939.

17. Hallock, P., and Rigler, L. G.: Chronic Cor Pulmonale, Staff Meet. Bull., Hosp. Univ. Minnesota **13**:106, 1941; Am. J. Roentgenol. **50**:453-460 (Oct.) 1943.

PATHOGENESIS IN PULMONARY VASCULAR DISEASE

In an evaluation of the various conditions producing cor pulmonale, it is much easier to explain the pathogenesis of some forms than of others. In primary pulmonary arteriolarsclerosis, pressure on the main pulmonary artery, organized pulmonary vascular thrombi and schistosomiasis of the lungs with pulmonary vascular changes, it is quite obvious that the diminution in the caliber of the blood vessels will lead to an increased resistance to the flow of blood that eventually will result in a strain on the myocardium of the right ventricle. However, in most of the cases, there is no significant primary vascular change that would account for the increased resistance to the flow of blood through the lungs.

In this series there was 1 case that was considered to be an instance of primary pulmonary arteriolarsclerosis. The patient was a 59 year old Russian-born man with a fifteen year history of cardiorespiratory distress. He was never bedridden throughout this period. He went rapidly into a state of congestive heart failure and died within several days. The pulmonary arterioles and arteries had advanced sclerotic changes with pronounced narrowing of the lumens. The heart weighed 475 Gm., and the myocardium of the right ventricle measured 0.9 mm. in thickness. Brill and Krygier [18] reviewed 20 similar cases collected from the literature and pointed out that in order to make this diagnosis on an anatomic basis every other factor that might lead to pulmonary hypertension and then act as a possible cause for the development of secondary pulmonary vascular sclerosis must be eliminated. Although emphysema is present in most of these cases, probably as a secondary nutritional change, the noticeable disproportion between the relatively small degree of emphysema and the extensive pulmonary vascular changes points to the latter as the important factor. The patient in our series was considerably older than the average patient encountered in a case of this type, who is usually 35. In 5 of the 20 cases reviewed by Brill and Krygier,[18] congestive heart failure developed and the patients died relatively rapidly. The same events occurred in our case. In the 20 cases, 50 per cent of the patients were women. This distribution is in contrast to that in cases of cor pulmonale resulting from emphysema, in which only an exceptional case is found involving a woman. The cause of primary pulmonary vascular sclerosis has never been determined. There is no apparent relation between generalized arteriosclerosis and arteriosclerosis in the pulmonary vascular bed. Ayerza's [19] original contention that syphilis is an important factor in

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18. Brill, I. C., and Krygier, J. J.: Primary Pulmonary Vascular Sclerosis, Arch. Int. Med. **68**:560-577 (Sept.) 1941.

the causation of this disease has never been substantiated. He also expressed the belief that the vascular changes were most likely secondary to primary bronchopulmonary disease. This is still an unsettled question.

In our series there was 1 case of cor pulmonale secondary to organized thrombi in the main pulmonary arteries. The patient was a 61 year old Negro man without any significant past history. Four weeks before his admission to the hospital he first noted the gradual onset of dyspnea on exertion. This became rapidly worse, and after an episode of syncope he became intensely dyspneic and died within three days with acute failure of the right side of the heart. The heart weighed 550 Gm.; the wall of the right ventricle averaged 1 cm. in thickness, and there was a large, firmly adherent, organized and partially recanalized thrombus present in the main pulmonary artery. This thrombus extended for a short distance into both the right and the left branches. The lumen of the main pulmonary artery was reduced to approximately one half. There were several smaller fresh thrombi in the smaller pulmonary arteries. The primary site of origin of these thrombi was not determined.

A similar case has been reported by Montgomery,[20] who also observed the extreme rarity of this condition. His patient was a 36 year old woman who died of acute right-sided heart failure after having evidence of such failure in varying degrees for a period of eleven months. Both in our case and in that of Montgomery, the cause for the formation of the thrombus could not be determined. In both cases there were no underlying vascular changes, nor was any site of origin for emboli discovered. In our case, although the clinical history was of short duration, the process undoubtedly had been going on for a long time, as evidenced by the advanced hypertrophy of the myocardium of the right ventricle and the well developed organization and recanalization of the thrombus in the pulmonary artery.

Other cases of the same type have been described by Balboni.[21] It is possible that primary pulmonary vascular sclerosis, described by Brenner,[22] may be the underlying factor in the formation of these thrombi.

19. Ayerza, L.: Ayerza's Disease: "Black Cardiacs," Rev. Soc. de med. int. **1**:73-83 1925.

20. Montgomery, G. I.: A Case of Pulmonary Artery Thrombosis with Ayerza's Syndrome, J. Path. & Bact. **41**:221-230 (Sept.) 1935.

21. Balboni, V. G.: Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Hypertrophy, New England J. Med. **223**:896-900 (Nov. 28) 1940.

22. Brenner, O.: Sclerosis of Pulmonary Artery with Thrombosis, Lancet **1**:911-914 (April 25) 1931.

Although not included in our consecutive series, a case of pulmonary schistosomiasis at Bellevue Hospital resulting in hypertrophy of the right ventricle has been reported in detail by Clark and Graef.[8] The patient was a 20 year old Puerto Rican youth, who complained of shortness of breath and swelling of the legs for one month prior to admission to Bellevue Hospital. His chief complaint on his admission was pain in the chest of three days' duration. Although rapidly digitalized, he became increasingly dyspneic and died twenty hours after his admission. The heart weighed 360 Gm., while the right ventricle measured 8 mm. in thickness and the left ventricle 10 mm. A chronic pulmonary arteritis had been produced by infection with Schistosoma mansoni. In the liver there was a nodular cirrhosis characteristically associated with this parasite. Shaw and Ghareeb,[9] in a review of 282 necropsies performed on patients with schistosomiasis, reported that in 33 per cent there was evidence of pulmonary infection and that 2 per cent of all patients died as a result of the ensuing right-sided heart failure. They described the pathologic picture in the lungs as beginning with an acute necroting arteriolitis that resulted from the action of the schistosome ova on the intima and media of the pulmonary arterioles. This was soon followed by an obliterative arteriolitis that later became recanalized. The new vessels became dilated, with resultant angiomatoid formation. This vascular change resulted in the obstruction to the flow of blood through the lungs.

Recently we have seen a case of syphilitic cardiovascular disease in which there was an aneurysm at the base of the aorta that compressed the pulmonary artery and resulted in hypertrophy of the right ventricle. This case, to be published in detail by Eichler,[6] was that of a 42 year old white man admitted to the hospital with signs of right-sided heart failure, who died shortly after his admission. Scott and Garvin [14] mentioned a similar case. In rare instances the aortic aneurysm, in addition to pressing on the pulmonary artery, may rupture directly into it (Delp and Maxwell [7]).

PATHOGENESIS IN PRIMARY DIFFUSE OBSTRUCTIVE EMPHYSEMA

In 40 of the 60 cases, pulmonary emphysema was considered to be the sole underlying pulmonary condition responsible for the development of the hypertrophy of the right ventricle. It has already been noted that among these cases only 1 of the patients is a woman and that the age incidence is higher than for the other types. These observations merely reflect the fact that advanced emphysema with considerable increase of the anteroposterior diameter of the chest is uncommon in women while it is of frequent occurrence in men past middle age. Furthermore, men in this age group are more often engaged in heavy manual labor than are women. For many years it

was thought that there was no direct relation between the pulmonary emphysema and the cardiac failure that was so often present in these cases. But in recent years it has been generally accepted that a close relation exists. There still remains, however, considerable speculation as to the exact mechanism whereby pulmonary emphysema produces hypertrophy of the myocardium of the right ventricle. Among the factors suggested have been pulmonary vascular sclerosis, diffuse fibrosis of the lungs, anatomic obliteration of some of the pulmonary vascular bed, the existence of vascular shunts between the systemic and pulmonary circulations, overfilling of the heart in emphysema, inspiratory pull on the pericardium and polycythemia.

The pulmonary arteriolarsclerosis that is found in some of these cases is generally considered to be a secondary change. It is often absent and when present is too insignificant in degree to be responsible for the primary increase of pulmonary vascular resistance (table 4). Parker,[23] in studying 32 cases of emphysema, found that pulmonary vascular changes were present in 80 per cent of the cases but concluded that there was no causal relation between this change and the hypertrophy of the right ventricle that was present in 72 per cent of his cases. In our series, pulmonary vascular sclerosis was present in 20 of 40 cases of emphysema and in only a few of these to a moderate or advanced degree (table 4).

Pulmonary fibrosis often accompanies emphysema of the lungs. However, like pulmonary arteriolarsclerosis, pulmonary fibrosis is not constantly present. It was present in only 16 out of the 40 cases of emphysema (table 4).

In order for the fibrosis to produce an increased resistance to the flow of blood through the lungs, it must of necessity be a diffuse and fine fibrosis that encircles the smaller blood vessels. The fibrosis following such conditions as silicosis and pulmonary tuberculosis is often a nodular, dense, localized fibrosis. Furthermore, in such a condition as tuberculosis, in which there is extensive destruction of pulmonary tissue, it has been demonstrated that the circulation to the diseased and fibrotic area is to a great extent taken over by the collateral capillaries coming from the bronchial arterial system, so that any effect of the fibrosis in these particular areas on the circulation does manifest itself in the systemic rather than in the pulmonary circuit. In the conditions in which diffuse and fine fibrosis do occur, as in acute diffuse interstitial fibrosis of the lungs, recently reported by Hamman and Rich,[12] and in acute silicosis resulting from exposure in talc and abrasive soap

23. Parker, R. L.: Pulmonary Emphysema: Relation to Heart and Pulmonary Arterial System, Ann. Int. Med. **14**:795-809 (Nov.) 1940.

industries, reported by Chapman,[24] there is not only arterial obstruction but also diffuse involvement of the smaller bronchioles resulting in obstructive emphysema. It is possible, therefore, that the pulmonary hypertension in part at least may be mediated through this mechanism. It has become a clinical habit when the diagnosis of emphysema is made to assume that fibrosis is always present—thus, the clinical usage of the term "fibrosis and emphysema of the lungs." This, however, is

TABLE 4.—*Relation Between the Weight of the Heart, Hypertrophy of the Right Ventricle, Degree of Emphysema, Pulmonary Arteriolarsclerosis, Diffuse Fibrosis of the Lungs and Bronchitis.*

Age	Sex	Weight of Heart, Gm.	Width of Right Ventricle, Cm.	Obstructive Emphysema	Pulmonary Arteriolar-sclerosis	Diffuse Fibrosis of Lungs	Bronchitis
62	M	350	0.6	3+	0	0	0
68	M	350	0.6	3+	0	0	1+
55	M	350	0.65	3+	0	0	2+
62	M	350	0.6	2+	0	0	0
71	M	380	0.7	3+	0	0	1+
55	M	390	0.9	4+	1+	1+	1+
70	M	390	0.7	4+	1+	0	1+
47	M	400	0.65	3+	0	0	0
70	M	400	0.8	4+	1+	1+	1+
64	M	400	0.7	3+	0	0	1+
57	M	400	0.6	3+	0	0	1+
67	M	400	0.7	3+	2+	1+	0
42	M	400	0.75	4+	1+	0	1+
55	M	400	0.6	4+	0	0	0
65	M	400	0.8	3+	0	2+	2+
80	M	400	0.8	3+	0	0	0
37	M	400	1.0	3+	1+	0	1+
88	M	400	0.8	3+	0	0	0
67	M	400	1.0	4+	0	0	1+
68	M	400	0.7	3+	0	1+	0
53	F	410	0.9	3+	0	1+	1+
54	M	410	0.8	3+	1+	0	1+
52	M	420	0.8	3+	1+	1+	0
67	M	420	0.8	4+	2+	2+	1+
61	M	420	0.8	4+	0	0	2+
45	M	440	0.6	4+	0	1+	2+
54	M	450	0.7	2+	1+	1+	0
69	M	450	1.3	3+	1+	0	1+
53	M	450	1.0	4+	0	0	1+
59	M	450	0.85	3+	1+	1+	1+
60	M	470	0.65	3+	0	1+	0
62	M	500	0.6	3+	0	0	2+
46	M	500	0.8	3+	1+	0	1+
55	M	520	1.0	3+	1+	0	0
57	M	540	1.1	4+	1+	0	2+
62	M	550	1.0	3+	3+	2+	0
64	M	570	0.9	4+	1+	0	0
60	M	600	1.0	3+	1+	1+	1+
68	M	770	1.4	3+	2+	0	0

not correct, since in many cases of emphysema there is practically no fibrosis present.

Anatomic obliteration of the pulmonary vascular bed as a result of pulmonary emphysema or other forms of pulmonary disease has also been offered as an explanation for the developing pulmonary hypertension. This, undoubtedly, is an important factor in increasing the

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24. Chapman, E. M.: Acute Silicosis, J. A. M. A. **98**:1439-1441 (April 23) 1932.

resistance to the flow of blood through the lungs. However, it is necessary to obliterate almost 80 per cent of the pulmonary vascular bed in dogs before any changes occur in the right ventricle (Lichtheim [25]). Furthermore, in these animals the remaining pulmonary tissue necessarily becomes emphysematous, so that the vascular bed is still further reduced. It must be pointed out that this experimental condition in animals is not applicable to human beings in that human beings often continue at hard laboring work over a period of years while the obliteration of the pulmonary vascular bed develops. Also, the resulting emphysema in the animals is not truly an obstructive emphysema but is one in which the lung expands to compensate for the increased space in the chest cavity. This experiment is somewhat analagous to the condition in a patient who has undergone a pheumonectomy, whose remaining lung becomes emphysematous in order to fill in the residual space. In addition, this type of patient would no longer engage in hard labor and would most likely be bedridden or lead a sedentary life. There are no studies available as to whether or not hypertrophy of the right ventricle developed in these patients. To what extent anatomic obliteration of the pulmonary vascular bed results in increased resistance to flow is not clear, because undoubtedly some readjustment of the circulation must take place whereby the volume of blood going through the affected lung or lungs is somewhat decreased, probably through vascular shunts, a greater amount of blood going to uninvolved portions, or else through a general readjustment between the systemic and pulmonary circulations.

Wood and Miller,[26] in a report of a series of injections of dye performed during studies of the relationship between the bronchial and pulmonary arterial circulations, mentioned the possibility of increased communications in the form of large vascular shunts between the two circulatory systems in pulmonary disease. These, they claimed, might allow a higher systemic pressure from the bronchial circulation to manifest itself in the pulmonary circuit with a subsequent strain on the right side of the heart, acting in the same manner as an arteriovenous fistula. These increased communications or shunts have not as yet been demonstrated in primary obstructive emphysema.

Compensatory polycythemia that occurs not infrequently in obstructive emphysema acts most likely only as a secondary aggravating factor in the development of pulmonary hypertension. About 80 per cent

25. Lichtheim, cited by Rehfisch: Zur Aetiologie der Vergrösserung der rechten Herzkammer, insbesondere bei behindeter Nasenatmung, Deutsche med. Wchnschr. **44**:227, 1918.

26. Wood, D. A., and Miller, M.: Role of Dual Pulmonary Circulation in Various Pathologic Conditions of Lungs, J. Thoracic Surg. **7**:649-670 (Aug.) 1938.

of the patients with emphysema have evidence of pulmonary hypertension in the form of pulmonary vascular sclerosis (Parker [23]). About 40 per cent of the patients with pulmonary tuberculosis also manifest some evidence of pulmonary hypertension in the form of hypertrophy of the right ventricle (Higgins [27]). Yet, polycythemia is surely not present in the same degree of frequency either in emphysema or in pulmonary tuberculosis. Zadek [28] pointed out that the severest grades of polycythemia vera may be encountered without any evidence of cardiovascular change. Fishberg [29] stated that the absence of high blood pressure in many cases of polycythemia vera shows that the augmented viscosity has had little effect on blood flow. He offered the explanation that the axial flow of red blood corpuscles in small vessels allows for only a layer of plasma to come into contact with the vessel wall, so that an increase in the number of red blood cells would not necessarily increase the resistance to the flow of blood. It is also of interest that Hess [30] could produce no cardiac hypertrophy by experimentally induced plethora, while Peacock [31] cited experiments which tended to show that increases of volume and of viscosity of the blood do not increase the blood pressure.

Kountz, Pearson and Koenig [32] found normal circulation times in dogs in which emphysema had been produced. They concluded from this fact that there was no increased resistance to the flow of blood through the lungs in emphysema. This conclusion appears to be unwarranted, because the circulation time does not necessarily reflect the degree of increased pulmonary vascular resistance but reflects rather the degree of heart failure. In systemic hypertension, in which there is often obvious increased peripheral vascular resistance, the circulation time is usually increased only when the heart begins to fail. The same is undoubtedly true of pulmonary hypertension and right-sided heart failure.

The explanation offered by Kountz, Alexander and Prinzmetal [33] that the hypertrophy of the heart occurs mainly in early stages of

27. Higgins, G. K.: The Effect of Pulmonary Tuberculosis upon the Weight of the Heart, Am. Rev. Tuberc. **49**:255-275 (March) 1944.

28. Zadek, I.: Die Polycythämien, Ergebn. d. ges. Med. **10**:355-400, 1927.

29. Fishberg, A. M.: Heart Failure, ed 4, Philadelphia, Lea & Febiger, 1940, p. 357.

30. Hess, L., and Saxl, P., cited by Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, p. 2392.

31. Peacock, H. A.: Blood Pressure and Blood Volume in Cases of Polycythemia Vera, Proc. Staff Meet., Mayo Clin. **4**:286-288 (Sept. 25) 1929.

32. Kountz, W. B.; Pearson, E. F., and Koenig, K. F.: Observations on Intrapleural Pressure and Its Influence on the Relative Circulation Rate in Emphysema, J. Clin. Investigation **11**:1281-1291 (Nov.) 1932.

emphysèma owing to a decreased negative intrapleural pressure with subsequent overloading of the heart is not supported by the clinical course in these cases. Cor pulmonale occurs not in the early stages but in the late and advanced stages of emphysema. Furthermore, once the diaphragm becomes fixed in its lowered position this overloading mechanism no longer operates, and one would naturally expect some alleviation, or at least a slower development, of the right-sided failure late in the disease. This again does not correspond with the usual clinical experience.

It appears more likely that there is an increased resistance to the flow of blood through the lungs in cases of advanced emphysema that over a period of time exerts a strain on the right side of the heart. There is much evidence to support this view. In the 40 cases in this series, primary obstructive emphysema was the only single constant feature, while, as has been mentioned before, the fibrotic and vascular changes were not present in every case, and when they were present it was usually in the more advanced stages, indicating that these were secondary rather than primary changes (table 4).

The lung in emphysema is in a constant state of overdistention. This is obvious at the time of postmortem examination, and often the lungs are found not only to fill the chest cavity completely but to bulge past the midline over the precordium. Furthermore, in pressure studies on large emphysematous bullae positive pressures are often encountered. Intrapleural pressure readings taken during the expiration on patients with emphysema usually range from — 1 or — 2 to + 2. These values tend to indicate that at least during the expiratory phase of the respiratory cycle there is an increased pressure above the normal within the lungs. Intrabronchial pressure studies taken at the same time reveal that this increased pressure is not reflected within the bronchial tree, since the readings taken were normal (Neergard and Wirz [34]). This, therefore, points to the site of increased pressure as being intra-alveolar rather than intrabronchial. It has also been demonstrated that increased intra-alveolar pressure exerts a direct effect on elevating pressure of the pulmonary vascular circuit. This was demonstrated by Maier [35] during the course of an intrathoracic surgical procedure. The patient in question was receiving anesthesia under positive pressure through a closed circuit. Pressure in this anesthesia circuit was deliberately raised. At the same time pressure recordings

33. Kountz, W. B.; Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, Am. Heart J. **11**:163-172 (Feb.) 1936.

34. Neergard, K., and Wirz, K.: Die Messung der Strömungswiderstände in den Atemwegen des Menschen in besondere bei Asthma und Emphysem, Ztschr. f. klin. Med. **105**:51-82, 1927.

35. Maier, H.: Personal communication to the authors.

were made of the pulmonary vascular circuit. It was noted that there was a direct relation between the pressure of the anesthesia circuit and the degree of elevation of the pressure of the pulmonary vascular system. The overdistended lung in emphysema, in which there is an increased alveolar pressure at least during the expiratory phase of the respiratory cycle, is within an enclosed and relatively fixed space, the thoracic cage. Thus, when this lung expands and exerts its increased pressure, it must do so at the expense of the compressible structures within the lung and chest. In turn, one notes that the diaphragm is pushed down; the rib spaces become widened; the anteroposterior diameter of the chest is increased, and the pulmonary parenchyma overlaps the precordium. The capillaries and smaller blood vessels within the lung are also compressible structures. It therefore seems reasonable that this increased pressure in the alveoli in cases of emphysema will also exert its pressure effects on the smaller blood vessels and capillaries coursing through the interalveolar septums. These pressure effects will increase the resistance to the flow of blood through these vessels, and, in turn, this increased resistance means more work for the myocardium of the right ventricle in order to maintain the normal cardiac output per beat. Eventually the burden will become so great that the right ventricle will become hypertrophied and may fail. This resistance to the flow of blood with the subsequent hypertrophy of the right side of the heart is therefore not necessarily based solely on the anatomic obliteration of the pulmonary vascular bed, as has been previously postulated, but, in addition, it is a functional pressure resistance relation occurring in functioning pulmonary tissue as exerted over a long period. Striking proof of this assumption is in the fact that cor pulmonale is infrequent in the advanced bullous forms of emphysema, in which there is pronounced anatomic obliteration of the blood vessels, while, on the other hand, it is relatively common in the finer diffuse forms of emphysema. Such associated phenomena as polycythemia that increases the viscosity of the blood, pulmonary arteriolarsclerosis, fibrosis impinging on the vessels, possible bronchopulmonary arterial shunts and overloading of the heart probably all play secondary and aggravating roles.

The question arises as to why cor pulmonale will develop in some cases of emphysema while in others it will not. The answer does not seem to be in any single factor, although Eppinger [36] tried to find one many years ago. He grouped the cases of obstructive emphysema into two types: those in which there was a primary bronchitis, in which cor pulmonale did not develop, and those in which there was no primary

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36. Eppinger, H.: Das Emphysem der Lungen, Vrtljschr. f. d. prakt. Heilk. 4:1-80, 1876.

bronchitis, in which cor pulmonale did develop. He stated that the collateral circulation between the pulmonary and the arterial systems that developed in those cases in which there was a primary bronchitis prevented any increased circulatory strain on the myocardium of the right ventricle. However, in our series there were a number of cases in which bronchitis had been present for at least thirty years (table 4). It would be difficult to say in these cases whether the bronchitis was primary or secondary, but at any rate it was present for a sufficiently long period that a collateral circulation could have developed. Nevertheless, cor pulmonale did develop in these cases. Similarly, according to Eppinger,[36] cor pulmonale should not have been present in those cases in which the emphysema was secondary to bronchiectasis, since there was sufficient collateral circulation developing over a period of time as a result of the underlying infection and the proliferation of granulation tissue. Here again, cor pulmonale was found. Furthermore, if such collateral circulation should develop to relieve the pressure, one would expect to see numerous dilated veins or venules in the region of the bronchi and bronchioles. These have not been observed. The answer as to why cor pulmonale develops in certain cases of emphysema and does not in others seems to lie in the interplay of many factors, such as the duration, severity and diffuseness of the emphysema, the age at the time of onset, the constitution of the patient, the absence or presence of infection and, most important of all, the type of present and past occupations. The proper combination of some or all of these factors in any person will result in a strain on the myocardium of the right ventricle. Parker[23] reported that in 72 per cent of the 32 cases of emphysema there was revealed evidence of hypertrophy of the right ventricle. Potentially, hypertrophy of the right ventricle can develop in any case of primary obstructive emphysema if the proper combination of factors is present.

PATHOGENESIS IN PULMONARY TUBERCULOSIS

The 2 patients with pulmonary tuberculosis associated with cor pulmonale were men, aged 63 and 39. Both revealed advanced pulmonary tuberculosis with widespread dissemination throughout both lungs, diffuse fibrosis and bilateral chronic obliterative pleuritis. Advanced emphysema was present, and there had been signs and symptoms of right-sided heart failure. The incidence of hypertrophy of the right ventricle in pulmonary tuberculosis varies in different reports from 4.6 per cent or even lower to as high as 40 per cent. This difference may be due to the variations in the postmortem methods of examination of the heart. When the gross measurement of the right ventricle is recorded without taking into account the general decrease of the size of the heart in tuberculosis, the incidence is usually found

to be low. On the other hand, if the technic of Herrmann [37] is employed, in which the right side of the heart is dissected away from the left side and the relative degree of hypertrophy of the two ventricles is taken into consideration, the incidence is much higher. This method was utilized by Higgins [27] in a recent study of the weight of the heart in tuberculosis. He also took into account the general decrease of the size of the heart as a result of the malnutrition and emaciation coincident with tuberculosis. In his study the incidence of hypertrophy of the right ventricle in association with pulmonary tuberculosis was reported as 40 per cent. Roberts and Lisa,[38] however, stated that the only reliable method for determining hypertrophy of the right ventricle is by histologic examination, and they found an incidence of 3 per cent.

Ackerman and Kasuga [39] found no definite correlation between the type and complications of tuberculosis and the incidence and degree of hypertrophy of the right ventricle, with the one exception that hypertrophy of the right ventricle was directly related to the duration of the tuberculosis. Such factors as obliteration of the pleural space, spontaneous or produced pneumothorax, far advanced pulmonary destruction, adhesions and kinking of the great vessels have all been suggested as possible underlying factors. Higgins [27] stated that none of these factors has a causal relation to development of cor pulmonale in pulmonary tuberculosis. He stated the opinion that the secondary emphysema resulting from fibrosis is the most likely etiologic factor.

In the 2 cases reviewed in our series all the aforementioned potential factors, with the exception of far advanced pulmonary destruction, were present. It was, therefore, impossible to draw any specific conclusions except that advanced destruction of the lung is apparently not necessary for the development of this process. Emphysema was advanced in both cases and may very well have been the important factor in the development of the hypertrophy of the right ventricle.

PATHOGENESIS IN BRONCHIAL ASTHMA

There were 6 cases of bronchial asthma in this series. Each of the patients had extensive diffuse emphysema. In these cases of bronchial asthma in which cor pulmonale developed it probably did so on the basis of associated emphysema. In bronchial asthma the presence

37. Herrmann, G. R.: Experimental Heart Disease: Methods of Dividing Hearts with Sectional and Proportional Weights and Ratios for Two Hundred Normal Dogs' Hearts, Am. Heart J. **1**:213-231 (Dec.) 1925.

38. Roberts, J. E., and Lisa, J. R.: Heart in Pulmonary Tuberculosis: Clinico-Pathological Study of One Hundred Autopsied Patients, Am. Rev. Tuberc. **47**: 253-262 (March) 1943.

39. Ackerman, L. V., and Kasuga, K.: Chronic Cor Pulmonale: Its Relation to Pulmonary Tuberculosis, Am. Rev. Tuberc. **43**:11-30 (Jan.) 1941.

of an increased intra-alveolar pressure, at least for temporary periods during outright asthmatic attacks, is much more obviously recognized than a constant expiratory increase of intra-alveolar pressure with long-standing emphysema. In the final analysis, however, the mechanism appears to be the same. Schiller, Colmes and Davis [40] analyzed a series of 15 cases of bronchial asthma studied at necropsy and found 5 in which there was a definite degree of hypertrophy of the right ventricle. Huber and Koessler [41] reported 2 cases of hypertrophy of the right ventricle in a series of 5 cases of bronchial asthma studied at necropsy. Both groups of observers noted that there was a direct relation among the duration, frequency and length of attacks of asthma, the degree of emphysema and the degree of hypertrophy of the right ventricle.

PATHOGENESIS IN SILICOSIS AND BRONCHIECTASIS

There were 6 cases of bronchiectasis and 3 of silicosis. In both of these conditions there were found both a focal and a diffuse fibrosis within the lungs. Nodular or focal fibrosis appears to be unrelated to the development of the emphysema. The fine fibrosis that surrounds the smaller bronchi often produces an extreme emphysema of the obstructive type. It is interesting to note that, particularly in cases of silicosis, the development of cor pulmonale is not parallel necessarily to' the degree of massive nodular fibrosis. It is rather more closely associated with the more diffuse, finer fibrosis. This association is obvious in such forms of silicosis as the acute forms developing after exposure to talc and asbestosis, in which the fibrosis tends to follow the bronchial tree and blood vessels rather than to occur in the nodular form. Therefore, most likely, in those cases of silicosis and bronchiectasis in which cor pulmonale develops it does so on the basis of the secondary emphysema that so often reaches an advanced state in these conditions. This assumption is probably also true of any other pulmonary disease in which a diffuse fine fibrosis results.

SUMMARY OF MORPHOLOGIC OBSERVATIONS

The salient morphologic changes were noted in the 60 cases studied at necropsy. The average weight of the heart was 460 Gm., with the smallest heart weighing 350 Gm. and the largest 770 Gm. The average thickness of the wall of the right ventricle was 0.8 cm., with the extremes of 0.6 and 1.4 cm. Although the dominant observation was

40. Schiller, I. W.; Colmes, A., and Davis, D.: The Occurrence of Cor Pulmonale in Cases of Bronchial Asthma, New England J. Med. **228**:113-117 (Jan. 28) 1943.

41. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**:688-760 (Dec.) 1922.

the hypertrophy of the right ventricle, the left ventricle in a number of instances was hypertrophied from a minimal to a moderate degree. Hypertrophy of the left ventricle in cor pulmonale may be explained on the basis of anoxemia. Smith and Bartels [42] produced cardiac hypertrophy in dogs by ligating the coronary arteries. Further evidence that impaired nutrition of the myocardium can lead to hypertrophy was present in a most unusual case described by Bland, White and Garland,[43] in which there was an anomalous origin of the coronary arteries from the pulmonary artery. It is known that the inhabitants of the mountain regions of Peru, where there is a lower concentration of oxygen in the atmosphere, consistently revealed generalized enlargement of the heart. Vacek [44] subjected a series of mice to an atmosphere in which there was a lowered oxygen content and also found consistent enlargement of the heart. Thus, it seems possible that the hypertrophy of the left ventricle can result from severe anoxemia that is so often present in emphysema. This may also account to a certain extent for some of the hypertrophy of the right ventricle.

Mural thrombi in the right atrial appendage were present in 6 instances; none was noted in the left atrium. Thrombi were found in the smaller branches of the pulmonary arteries in 5 instances. Whether or not these were embolic or stasis thrombi was not determined. In 6 cases the tricuspid ring was noticeably dilated.

The liver and spleen were constantly the site of varying degrees of chronic passive congestion. In 3 of the cases there was cardiac cirrhosis. Thus, there was an incidence of cardiac cirrhosis of 5 per cent, whereas in chronic passive congestion of the liver associated with all forms of heart failure the incidence is usually lower (Boland and Willius [45]). The cases of cor pulmonale associated with cardiac cirrhosis were of long duration with several episodes of decompensation. Varying degrees of ascites were commonly observed. In only 3 cases was a right-sided pleural effusion demonstrated at the time of necropsy.

The other significant changes were related to the underlying pulmonary disease. In the cases of emphysema these changes consisted of varying degrees of fibrosis, pulmonary arteriolarsclerosis and chronic

42. Smith, H. L., and Bartels, E. C.: Gross Cardiac Hypertrophy in Myocardial Infarction, Am. J. M. Sc. **184**:452-455 (Oct.) 1932.

43. Bland, E. F.; White, P. D., and Garland, J.: Congenital Anomalies of Coronary Arteries, Am. Heart J. **8**:787-801 (Aug.) 1933.

44. Vacek, T.: Functional Adaptation of the Heart in Mice Living Under Insufficient Oxygen Supply, Arch. f. d. ges. Physiol. **212**:357-364, 1926.

45. Boland, E. W., and Willius, F. A.: Changes in Liver Produced by Chronic Passive Congestion with Special Reference to the Problem of Cardiac Cirrhosis. Arch. Int. Med. **62**:723-739 (Nov.) 1938.

bronchitis, in addition to the far advanced emphysema. The other underlying pulmonary conditions, such as bronchiectasis, silicosis and tuberculosis, were present in the incidence indicated in table 1.

The relation between chronic bronchitis and emphysema was of special interest. In the 40 cases of diffuse obstructive emphysema, there was some anatomic evidence of inflammatory change in the bronchial tree in 75 per cent of the cases. Whether or not this close relation points to bronchitis as a possible factor in the development of the emphysema or whether bronchitis is purely a secondary phenomenon occurring in a lung with lowered resistance cannot be answered at the present time. In relation to this close association of bronchitis and emphysema, it was noted clinically that in a majority of these cases a cough productive of a white mucoid sputum was an early and constant occurrence.

Since cases of obvious coronary atherosclerosis were excluded from this study, the fact that there was only a minimal occurrence of atherosclerosis despite the fact that the cases represented an older age group is of no significance whatsoever. The degree of aortic atherosclerosis was typical of the age group studied and bore no relation to the degree of pulmonary vascular sclerosis.

CLINICAL PICTURE

Brill,[46] in analyzing the clinical picture of cor pulmonale, divided the clinical course into two phases: the early pulmonary phase, in which the signs and symptoms of the underlying pulmonary disease predominate, and the later cardiac phase, in which the signs and symptoms of failure of the right ventricle are manifest. In the first phase, one usually finds the dyspnea, hemoptysis, cyanosis, polycythemia and clubbing of the fingers, which are dependent on pulmonary insufficiency, in addition to the more or less specific signs and symptoms of the primary pulmonary lesion; while in the second phase, the engorged veins of the neck, enlarged liver, generalized edema, increased venous pressure and slowed circulation time are the obvious observations.

The transition from one phase to the other is often undetected, since the dyspnea and cyanosis, the early symptoms of cardiac failure, are also the symptoms manifested by the underlying pulmonary disease. Whereas in most forms of heart failure the onset of a break in myocardial reserve is heralded by the appearance of dyspnea, patients with cor pulmonale usually have been dyspneic and cyanotic for many years as a result of pulmonary insufficiency. However, an increase in these symptoms or the appearance of orthopnea in a person who previously

46. Brill, I. C.: The Clinical Manifestations of the Various Types of Right-Sided Heart Failure (Cor Pulmonale), Ann. Int. Med. **13**:513-522 (Sept.) 1939.

could lie flat may be indicative of a break in compensation. Similarly, an intensification of the cyanosis already present far out of proportion to the dyspnea is of great significance in the detection of an early break in myocardial reserve. Cyanosis is more intense in patients with cor pulmonale with cardiac failure than in those with any other form of heart disease; hence, the term "black cardiacs."

In most of the cases reported in this series, the presenting complaint on the patient's admission to the hospital was an increase in the shortness of breath that had been present in a milder degree for many years. In a few, the presenting complaint for which the patient sought admission was swelling of the ankles. Seven patients had a chief initial complaint of precordial pain; in 1 of these the pain was associated with syncope. Of these 7 patients, 1 had burning pain over the left pectoral region for a period of four days prior to his admission. This was associated with dyspnea. Another complained of pain in the chest for several months, also associated with intense dyspnea. The remaining 5 patients had precordial pain, the duration of which ranged from ten to fourteen days. In 2 of these, however, the pain seemed to be of pleuritic rather than of cardiac origin. In examination of none of these patients with precordial pain was any electrocardiographic evidence of coronary occlusion with myocardial damage demonstrated, nor did postmortem examination reveal any significant degree of coronary sclerosis or myocardial fibrosis. The intense cyanosis raises the question whether myocardial anoxemia might have been responsible for the pain.

While in most cases the onset of cardiac failure was insidious, in a fair number there were manifested more or less acute episodes of cardiac failure. The precipitating factors in these cases were intercurrent infections of the respiratory tract, attacks of asthma and, in 1 case, a carbuncle of the neck. The patients usually complained of rapidly increasing dyspnea. Some complained of pain in the epigastrium, in 1 case so severe and associated with such an acute tenderness of the liver that the diagnosis on admission was acute cholecystitis. A few complained of syncope, while 2 patients were brought in to the hospital in coma.

In the cases of severe acute cor pulmonale, the most striking features on physical examination are the intense "black cyanosis," chiefly of the lips and also of the nail beds and skin; the prominent eyes, giving rise to the term "froglike" in our service; the suffused and watery condition of the conjunctivas, resulting from the intense chemosis; the purplish tongue, usually also dry as a result of continued mouth breathing, and the usually full and prominent veins of the neck, in which pulsation is rare. In obese patients whose veins of the neck are deep seated, this feature may not be noted.

In most of our cases emphysema was the underlying pulmonary condition, and in these there was a disproportionate increase in the anteroposterior diameter of the chest over the transverse diameter. The physical signs in the lung were dependent on the morphologic changes present. In none of the cases was a pleural effusion detected clinically. The cardiac borders were difficult to detect by percussion, so that in most of these cardiac enlargement could not be determined on physical examination. Similarly, a point of maximum impulse was frequently absent or was displaced to the epigastrium, where the pulsations of the inferior surface of an enlarged right ventricle could be palpated.

The cardiac sounds were usually distant when emphysema was present. In the vast majority the second pulmonic sound was accentuated. In 7 cases, however, the aortic second sound was greater than the pulmonic. In one third of the cases systolic apical murmurs were heard, to which no clinical significance was attributed. In 2 cases transient systolic and diastolic murmurs were heard over the pulmonic area by various observers, so that in 1 of these the diagnosis of congenital heart disease was entertained. Whether these were caused by functional pulmonary arterial dilatation or were the result of increased tension within the pulmonary circuit could not be definitely ascertained. Auricular fibrillation was present in only 9 instances. The blood pressures ranged from 100 to 160 systolic and from 60 to 100 diastolic. As has been previously stated, the cases in which higher pressures were encountered were deliberately eliminated.

The liver was palpably enlarged in most of the cases, and in those in which the cardiac failure was rapid it was frequently tender. Ascites was noted in those cases of chronic failure. Edema of the ankles was present to varying degrees, depending on the degree and duration of cardiac failure. Clubbed fingers were definitely present in 19 of the 60 cases, while in a smaller number early changes, such as downward curvature of the finger nails, were observed.

LABORATORY OBSERVATIONS

Laboratory data available on the clinical material studied revealed no single consistent diagnostic test. The most significant changes appeared in the erythrocyte count. Polycythemia was present in 14 of the 39 cases in which blood counts were made. The extremes ranged from 3,300,000 to 6,500,000, with an average of 4,960,000. These values must be considered in the light of the following limitations. The determinations were performed over a period of years by various persons, giving rise to a considerable margin of error as a result of individual variation in technic. In addition, most of our patients come from the low income districts, and the effect of nutritional

inadequacy must play a part. Weber,[47] in a study of secondary poly-
cythemia, reported counts as high as 10,000,000. In our own experi-
ence, in a few cases of cor pulmonale not reported in this series, we
have seen similar high counts. There appeared to be no correlation
between the onset or degree of failure and the degree of polycythemia.
While polycythemia frequently accompanies cor pulmonale, it need not
necessarily be present in order for the diagnosis to be made.

Such tests as studies of circulation time and recordings of venous
pressure were not performed as a routine. The circulation times,
whenever studied, were elevated and correlated well with the degree
of failure. Kountz and Alexander [48] recorded that the venous pressure
was consistently elevated in emphysema alone. In our experience,
the determination of venous pressures in these cases proved of ques-
tionable value. For many patients with extreme degrees of failure of
the right ventricle whose circulation times were increased, the record-
ings of venous pressure were normal or even lower. The chief difficulty
arises from the fact that it is hard to establish an accurate base line
at the level of the auricle in patients with extreme emphysema.

Roentgenographic studies of the chest revealed the expected and
typical changes in the pulmonary parenchyma associated with the under-
lying pathologic pulmonary condition. The cardiac silhouette, on the
other hand, showed great variations. In a relatively small number,
the cardiac shadow showed definite evidence of enlargement and altera-
tions in the cardiac borders consistent with an enlarged right ventricle.
In these cases the left cardiac border showed either straightening or
prominent convexity in the area of the pulmonary artery in the postero-
anterior view, and fluoroscopic examination revealed the associated
displacement of the point of opposite impulse delineating right from
left ventricle thrusts in an apical direction. These classic roentgeno-
graphic findings in cor pulmonale were seen in those cases in which
the underlying pulmonary change was at a minimum as compared
with the interference with the pulmonary circulation, that is, in the case
of primary pulmonary arteriolarsclerosis and in the cases of pulmonary
fibrosis with relatively little pulmonary emphysema.

However, in the great majority of cases in this series, the classic
roentgenographic picture of cor pulmonale was masked or hidden by
the alterations in the chest created by extensive emphysema, fibrosis,
pleural obliteration or kyphoscoliosis. In the cases of emphysema, the
depression of the diaphragm resulted in an elongation of the medi-
astinum, so that the heart appeared smaller than normal and the normal

47. Weber, F. P.: Secondary Forms of Polycythemia Rubra—Ayerza's Dis-
ease, Brit. M. J. 2:658-660 (Oct. 30) 1920.

48. Kountz, W. B., and Alexander, H. L.: Emphysema, Medicine 13:251-316
(Sept.) 1934.

cardiac contours were obliterated. The increase in lateral diameter of the chest resulting from the elevation of the thoracic cage associated with emphysema made the determination of the cardiothoracic ratio spurious. Nevertheless, in a large number of cases of this kind, even minor changes in the cardiac silhouette seen on fluoroscopic examination were of significance. Prominence of the area of the pulmonary artery or of the outflow portion of the right ventricle in the right anterior oblique position or displacement toward the apex of the point of opposite pulsation were the only changes indicative of enlargement of the right ventricle. Parkinson and Hoyle,[19] in a careful study of the pulmonary conus in emphysema, found evidence of dilatation on roentgenograms in 80 per cent of their cases. In none of our cases was enlargement of the left auricle, as evidenced by displacement of the barium-filled esophagus, noted.

Electrocardiographic tracings were available in 21 of the 60 cases in this series. In all of these, cardiac failure was present at the time the tracings were made. Voltage was low in 12 cases, moderately low in 4 and normal in 5. The most notable change was in the direction of electrical axis deviation. In 14 of the 21 cases definite deviation of electrical axis to the right was shown, while in 3 others there was revealed a tendency to deviation of the axis to the right, as evidenced by relatively deep S waves in lead I. In 3 cases there was no deviation of the axis, while in 1 case of paroxysmal ventricular tachycardia deviation of the axis to the left occurred just prior to the death of the patient.

DIAGNOSIS

It is significant that in not one case in this series was the diagnosis of cor pulmonale established or entertained prior to the onset of the symptoms and signs of cardiac failure. In all fairness, however, it should be stated that a great number of the patients did not seek medical attention until the distress of cardiac failure appeared.

It is obvious that from the point of view of treatment it is extremely important to detect the presence of cor pulmonale early, so that measures can be taken to ward off the development of cardiac failure. In this connection, it might be helpful to investigate routinely the cardiac status of all patients with chronic pulmonary disease and emphysema. Careful observations of physical signs indicative of increase in size of the right side of the heart, such as prominent impulse in the epigastrium and accentuation of the second pulmonic sound as well as careful ronetgenographic and fluoroscopic studies, are of great value. The presence of right axis deviation or the development of a deep

49. Parkinson, J., and Hoyle, C.: Heart in Emphysema, Quart. J. Med. **6**:59-86 (Jan.) 1937.

S wave in lead I, indicating a tendency toward right axis deviation, is of extreme value in establishing the diagnosis. In this connection the use of the special lead, as recommended by Goldberger,[50] for determining early changes in the right ventricle might be helpful.

Even after the development of cardiac failure, the diagnosis of cor pulmonale is too often missed. The suddenness of onset with severe dyspnea and precordial pain often leads to the erroneous diagnosis of coronary occlusion. In our series, this occurred 4 times. However, the evidences of purely right-sided failure, the "black cyanosis," the chemosis and edema of face and neck as well as the presence of emphysema or other extensive pulmonary disease, should suggest the diagnosis of cor pulmonale. Add to these the presence of polycythemia, deviation of the electrical axis to the right and absence of changes indicative of myocardial infarction on the cardiogram, and the diagnosis should be easily established.

Occasionally, in the presence of failure, murmurs appearing over the pulmonic area, both systolic and diastolic, have given rise to the erroneous diagnosis of rheumatic or congenital heart disease. In this series these diagnoses were made once each. In such cases the disappearance of the murmurs when compensation is restored and the absence of any cardiographic evidence of an enlarged left auricle should correct the error.

In this series the most common error in diagnosis was simply to denote them as cases of arteriosclerotic heart disease. This diagnosis was made in 26 cases. All too often this diagnosis is one of exclusion; that is, if congenital, rheumatic, hypertensive or thyrotoxic causes for heart disease are excluded, then arteriosclerosis remains. As all the patients in these cases were in the older age group, arteriosclerosis appeared to be a logical diagnosis. The occurrence of this error in almost 50 per cent of the cases serves only to emphasize the importance of considering chronic pulmonary disease as a significant etiologic factor in heart disease.

Of the 60 cases in this series, the correct diagnosis was made antemortem in 24 instances. It is interesting to note that the accuracy of diagnosis was greater in the more recent cases, indicating the increasing recognition of cor pulmonale in recent years.

CLINICAL COURSE, DURATION AND TYPE OF FAILURE

As mentioned previously, in none of the cases of cor pulmonale was the condition recognized prior to the onset of cardiac failure. Cardiac failure, predominantly of the right side, is the classic cardiac manifesta-

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50. Goldberger, E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, Bull. New York Acad. Med. **20**:419-420 (July) 1944.

tion of the disease. The duration and number of episodes of cardiac failure were investigated. In 50 of the 60 cases the histories were adequate for study. Of the 50, it is significant that in 30 there was but one episode of cardiac failure, which terminated in death. It is difficult to describe each case in detail, but the composite picture is that of a person who has had chronic pulmonary disease for many years and in whom, over a period of but a few days to a week, an accentuation of cough rapidly developed. Many noted pain in the precordial or anterior area of the chest and a few noted pain in the upper part of the abdomen. Edema of the ankles, legs and thighs developed fairly rapidly soon after that. When brought to the hospital, these patients were acutely ill and in severe respiratory distress. Cyanosis was intense, and they fitted the descriptive term of "black cardiacs." Their faces were suffused; their eyes were injected and moist, and they were extremely restless and difficult to manage. In fact, some were definitely psychotic as a result of the cerebral anoxia. It is significant

TABLE 5.—*Incidence of Episodes of Failure*

Number of Patients	Episodes of Failure
30	1
11	2
1	3
2	4
4	0 (Died of encephalitis, meningitis and pneumonia)
10	? (Undetermined number, language difficulty, coma, etc.)

that there seemed to be more than a coincidental relation between the administration of a sedative and the occurrence of death in a few cases.

In 7 of these cases, death occurred within a period of one to three days from the onset of failure, while in the remainder the duration of life varied from three weeks to six months. The mode of death for most of the patients was gradual, although a large number died relatively suddenly. It was commonly observed that while clinically the patients appeared to be comfortable, or even at times improving, they died suddenly, for no apparent reason. This observation was also made by Scott and Garvin[14] and by Brill.[46]

Eleven patients had two episodes of failure prior to death, while 1 had three and 2 four such episodes. In some of these cases there were intervals of as long as two years between episodes of failure, while in 1 case a period of five years elapsed before death occurred. These cases indicate the importance of the interrelation between pulmonary insufficiency and cardiac failure, for the cardiac insufficiency was probably secondary to the anoxia produced by an intercurrent

pulmonary pathologic process, such as bronchopneumonia. When this subsides, cardiac compensation can often be restored and maintained as long as pulmonary ventilation and respiratory exchange is adequate.

The type of failure in all the cases was predominantly right-sided failure, with the exception of 3 cases in which paroxysmal nocturnal dyspnea was present. This evidence of additional left-sided failure may be attributed to unrecognized sclerosis of the smaller coronary vessels, to the possibility of an unrecognized preexistent hypertension or else to the fact that in cor pulmonale the patient often suffers from a severe degree of chronic anoxia, which reflects itself in an insufficient oxygenation of the blood that, in turn, results in anoxemia of both ventricles.

TREATMENT

The management of cor pulmonale resolves itself basically into the prevention and treatment of anoxemia. It is apparent, therefore, that all efforts should be made to promote the efficiency of the respiratory mechanism and to minimize so far as is possible the damage already present in the lungs.

It is beyond the scope of this paper to discuss the treatment of the various types of pulmonary lesions which may play a part in the causation of cor pulmonale. Nevertheless, it is important that all patients with bronchial asthma, chronic bronchitis, bronchiectasis and suppurative pulmonary infection be treated vigorously early in the course of the disease in order to prevent the development of hypertrophy of the right ventricle. The management of these conditions has been ably described by other authors dealing with these subjects.

When pulmonary emphysema and pulmonary fibrosis have been established, efforts should be directed toward the improvement of respiratory exchange and the prevention of bronchial and pulmonary infections. In this regard, it is important that these patients be impressed with the fact that all of the infections of the respiratory tract, no matter how mild they may appear to be, should not be treated lightly. These patients should be cautioned against undue exposure to inclement weather and to crowds during epidemic times. As most of our patients seem to have done better during the summer months, it would appear wise whenever possible to send them to less rigorous climates during the winter months. For some, a permanent relocation in a milder climate may do more to lengthen their lives than any other procedure.

For obese patients with considerable dyspnea and emphysema, the use of an abdominal belt may add considerably to their comfort.

As was pointed out elsewhere in this paper, it is often difficult to determine clinically in cases of cor pulmonale the onset of cardiac failure. Consequently, in recent years we have been digitalizing our patients before the signs of right-sided failure become manifest. In this way,

we feel that we may be delaying somewhat the onset of cardiac insufficiency. When the signs of right-sided failure appear, the patient is immediately placed on a regimen of a salt-free diet and restricted fluids, and diuretics are administered when necessary.

Cardiac failure in cor pulmonale is often acute, and death may occur within a few days. These cases should be treated as emergencies, and all measures aimed at combating anoxemia and cardiac failure should be taken without delay. Oxygen is vitally important and, in our experience, is best administered under positive pressure in high concentration by means of a special mask. Digitalization should be immediate and complete. Diuretic measures should be administered vigorously. Mercurial diuretics can be used freely and administered once daily if necessary. When polycythemia is evident, withdrawal by phlebotomy of 500 to 1,000 cc. of blood may be a life-saving procedure.

As indicated elsewhere in this paper, these patients are usually extremely restless and often disoriented. Sedation must be used with extreme caution. Morphine and codeine are to be avoided assiduously. Many patients may appear more comfortable after their administration, but few recover afterward. By suppressing the cough reflex, the purulent bronchial secretions are permitted to puddle in the pulmonary tree, further increasing anoxemia. Paraldehyde is not recommended, because it is largely excreted by and is irritating to the lungs. Chloral hydrate and barbiturates may be used with caution if it is remembered that in older patients the sedatives of the latter group may be exciting. In the final analysis, the cerebral manifestations result from cerebral anoxemia, which will be relieved only after measures aimed at combating the pulmonary infection and cardiac failure take effect.

COR PULMONALE AND OTHER CARDIAC DISEASE

This paper has dealt with cases of cor pulmonale unassociated with other cardiac disease. In the past ten years, we have become more and more impressed with the prevalence of this condition both clinically and in the autopsy room. Only too often the attention of the clinician and pathologist is diverted by the presence of hypertension or coronary arteriosclerosis as the primary factor in a given case, so that the cor pulmonale which may also be present is minimized or completely overlooked. In many of these cases, a review of the clinical history will often reveal that the cor pulmonale, with its associated pulmonary lesion, played a relatively larger part in the symptoms and disability than the coincidental hypertension or arteriosclerosis. It is evident from the statistics presented in this paper that the greater number of cases of cor pulmonale occur in the same age group that is subject to both hypertension and arteriosclerosis.

SUMMARY

Sixty consecutive cases of cor pulmonale unassociated with other forms of heart disease were studied at necropsy.

The underlying etiologic factors may originate primarily in the bony thorax, in the pulmonary vascular tree or in the pulmonary parenchyma.

Diffuse obstructive emphysema, either primary or secondary to such diseases as pulmonary tuberculosis or silicosis, was considered to be the significant underlying pulmonary factor in the vast majority of the cases.

Diffuse obstructive emphysema was thought to produce a changed pressure relation within the alveoli and in this manner result in an increased resistance to the flow of blood to the lungs. This change was considered to be a primary mechanism in the development of cor pulmonale, while such associated factors as anatomic obliteration of the pulmonary vascular bed, fibrosis of the lung, compensatory polycythemia and overfilling of the heart were considered to be secondary aggravating factors of varying significance.

The clinical course in these 60 cases was studied, and the difficulty and importance of diagnosis in the prefailure stage was emphasized.

Treatment of cor pulmonale was considered in general terms.

ABNORMALITIES IN THE ELECTROCARDIOGRAM FOLLOWING HEMOLYTIC STREPTOCOCCUS SORE THROAT

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A N extensive study has been made recently of acute hemolytic streptococcic disease of the respiratory tract among military personnel. A summary of the clinical and bacteriologic observations, so far as they contribute to the understanding of the etiology and pathogenesis of rheumatic fever, has been published.[1] The data indicated (1) that rheumatic fever was invariably preceded by infection by group A hemolytic streptococci; (2) that a nonarthritic nonsuppurative continuing disease also frequently followed infection by these organisms, and (3) that electrocardiographic abnormalities, indicating the presence of carditis, were often present during the course of arthritic and nonarthritic illness.

It is the purpose of this paper to illustrate and describe the electrocardiographic abnormalities that were discovered and to compare them with those previously observed during the course of streptococcic and other types of infectious disease.

MATERIAL AND METHODS

All patients suffering from disease of the respiratory tract were seen by one of us; a history was obtained, a physical examination performed and culture materials taken from the throat.[1a] Patients discovered on clinical and bacteriologic grounds

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The facilities of the Department of Medicine, Stanford University School of Medicine, San Francisco, were made available to the commission for certain purposes.

These studies were made during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

1. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945.

1a. Serial antibody determinations were made in nearly all these cases. A significant antistreptolysin and/or antifibrinolysin response occurred in approximately 87 per cent.

to be infected by group A hemolytic streptococci were studied by a variety of laboratory procedures. Most important, from the standpoint of this report, were serial determinations of the erythrocyte sedimentation rate (Westergren) and electrocardiograms, each of which was obtained on approximately the ninth and twenty-first days of the illness and more frequently and for a longer period in many instances. Certain patients have been included for whom this program was not followed precisely. No patient received digitalis.

RESULTS

Detailed serial observations were available on 185 patients with acute hemolytic streptococcic disease of the respiratory tract, approxi-
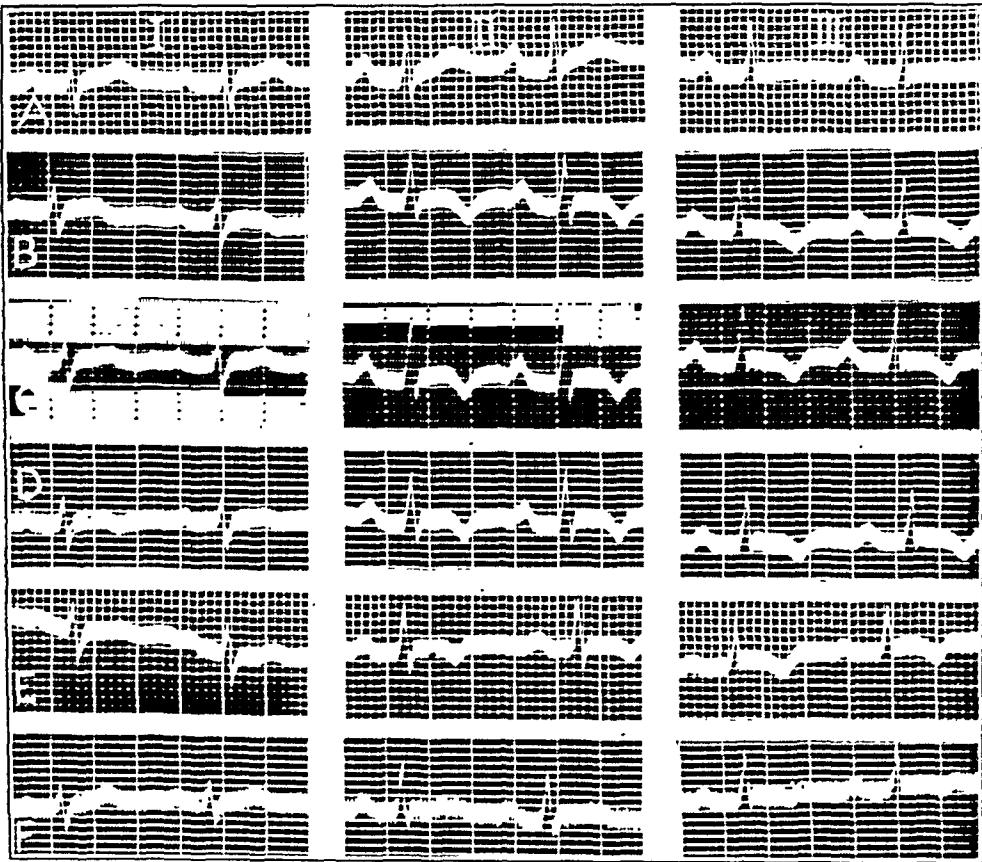

Fig. 1 (case 1).—Nonarthritic continuing disease. There was prolongation of the PR interval on the ninth day and later. There were progressive changes in the T waves, with flattening in lead I and inversion in leads II and III followed by a return toward normal. *A*, the ninth day, with the erythrocyte sedimentation rate 86 mm. per hour. *B*, the fifteenth day, with the erythrocyte sedimentation rate 90 mm. per hour. *C*, the twentieth day, with the erythrocyte sedimentation rate 84 mm. per hour. *D*, the twenty-fourth day, with the erythrocyte sedimentation rate 42 mm. per hour. *E*, the thirty-third day, with the erythrocyte sedimentation rate 24 mm. per hour. *F*, the forty-first day, with the erythrocyte sedimentation rate 23 mm. per hour.

mately 50 of whom exhibited signs of an arthritic or nonarthritic continuing disease. Definite electrocardiographic abnormalities were discovered in 31, and these patients are the subjects of this report.

Pertinent Data in Thirty-One Cases of Hemolytic Streptococcus Disease of the Respiratory Tract in which Abnormalities of the Electrocardiogram Were Demonstrated

Case Number	Acute Sore Throat					Arthritis		PR Interval		T Wave	Comment
	Day First ECG	Days Afebrile First ECG	Day First Abnormal ECG	Duration of ECG Abnormality in Days	ESR Abnormal in Days	Present	Days ECG Abnormal Before Appearance	Maximum Duration Observed in Seconds	Minimum Duration Observed in Seconds		
1	9	4	9	28	>11	No	—	0.24	0.18	Inverted in leads I, II, III	Illustrated
2	12	3	12	>20	>20	No	—	0.24	0.21	Normal	
3	10	4	10	>7 <25	<15	No	—	0.18	0.18	Inverted in leads I, II, III	Illustrated
4	28	20	28	<11	45	No	—	0.21	0.16	Normal	
5	9	6	9	<18	<21	No	—	0.14	0.11	Flat, lead II; inverted, lead III	T waves became upright in leads II and III during convalescence
6	13	4	32	>12	>15	No	—	0.21	0.16	Normal	Illustrated
7	9	3	9	10	20	No	—	0.16	0.16	Flat, lead I; inverted, II and III	
8	7	4	7	>21	>28	No	—	0.21	0.21	Normal	
9	24	F	24	>19	43	No	—	0.36	0.24	Normal	Illustrated
10	13	10	13	>20	>33	No	—	0.26	0.22	Normal	
11	14	2	11	>8	<21	No	—	0.24	0.24	Normal	
12	8	6	8	>14	15	No	—	0.16	0.16	Inverted in leads II and III	T waves became upright in leads II and III during convalescence
13	9	F	9	>24	>28	No	—	0.24	0.10	Inverted in leads II and III	Illustrated

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No.							Fever				T waves	Remarks
14	11	8	11	17	<13	>30	No	—		0.16	Normal	ECG remained abnormal through 36th day
15	11	8	9	29	<7	>45	No		0.21	0.16	Normal	Continuing illness with fever
16	8	22	13	8	>36	>36	No		0.22	0.16	Inverted in leads I, II, III	No ECG obtained between 9th and 40th days
17	9	5		25	<19	>44	No	—	0.16	0.16	Normal	
18	9	F	F	40	?	>40	No		0.22	0.16	Normal	T waves, leads II and III, upright on 25th day
19	13	9	13	13	>38	>50	No	—	0.21	0.16	Normal	
20	13	9	13	13	<11	<10	No		0.24	0.24	Flat in lead II; inverted lead III	T waves of high voltage by 12th day
21	38	34	38	38	7	>39	No		0.24	0.24	Normal	
22	8	5	8	8	3	<12	No	—	0.18	0.18	Flat in leads I, II and III	
23	8	F	F	14	>10	50	Yes	N.D.	0.36	0.16	Normal	Moderately severe rheumatic fever
24	10	F	F	23	70	90	Yes	60	0.28	0.16	Inverted in leads I, II and III	Illustrated
25	19	F		19	>7	45	Yes	N.D.	0.24	0.16	Normal	Severe rheumatic fever
26	36	16		36	50	85	Yes	27	0.16	0.16	Flat, lead I; inverted II and III	Illustrated
27	10	4	10	10		70	Yes	0	0.24	0.16	Normal	Mild rheumatic fever
28	7	5	7	7	35	40	Yes	5	C.B.	0.16	Flat, leads I and II; inverted, lead III	Illustrated
29	—	—	—	—		—	Yes		0.24		Normal	
30	9	6	9	9	8	70	Yes	N.D.	0.24	0.16	Inverted, leads I, II and III	Repeated sore throats before onset of rheumatic fever; several relapses
31	9	9	>150	35		45	Yes	6	0.16	0.16	Normal	Severe rheumatic fever with pericarditis
36	F	F	30	35	45	70	Yes	N.D.	0.36	0.16	Normal	Mild rheumatic fever

Explanation of abbreviations: N.D., not done; F, fever; C.B., complete block.

The essential data are presented in the table. Only a prolongation of
the PR interval to more than 0.2 second was regarded as significant
under any circumstances. Unless the conduction time was demon-
strated on either previous or subsequent occasions to be at least 0.05
second less, a PR interval of 0.24 second was required as an index of
abnormality. Changes in the elevation of the RS-T segment were
ignored. The T waves were regarded as normal unless they were
completely flat or inverted in leads I or II. Variations in the form
of the T wave in lead III were not considered unless one or both of
the other leads exhibited abnormalities. Precordial leads were not
utilized.

The application of these relatively rigorous criteria has eliminated
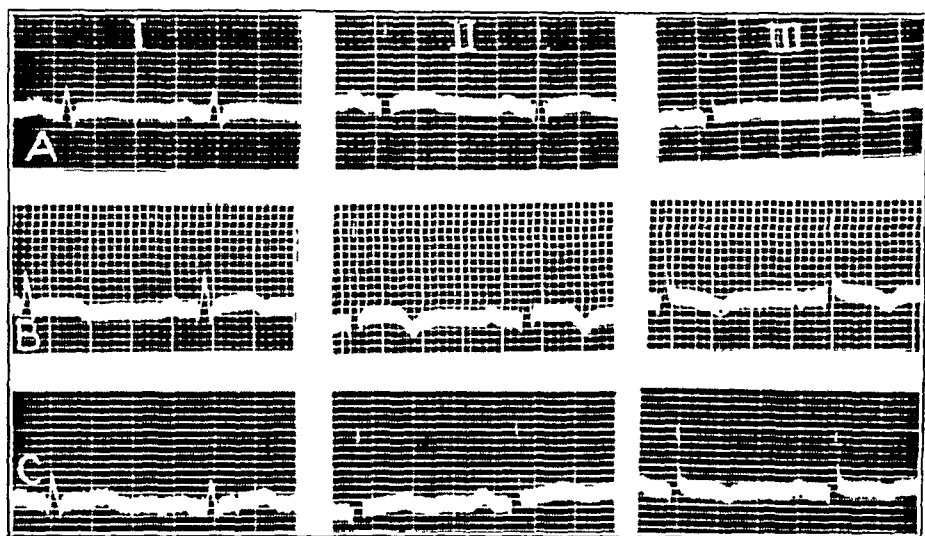certain cases in which the electrocardiogram would usually be regarded

Fig. 2 (case 3).—Nonarthritic continuing disease. *A,* the tenth day, with the
erythrocyte sedimentation rate 84 mm. per hour. The T waves were flattened in
all leads. *B,* the sixteenth day, with the erythrocyte sedimentation rate 11 mm.
per hour. The T waves were inverted in all leads. *C,* the thirty-fifth day, with the
erythrocyte sedimentation rate 10 mm. per hour. The T waves were of low voltage
but were upright in leads I and II and inverted in lead III.

as abnormal. It was believed that the technic of interpretation described
here would be more clearcut and less controversial.

Nonarthritic Continuing Disease. — Abnormal electrocardiograms
were obtained for 22 patients with nonarthritic, poststreptococcic con-
tinuing disease. In 15, there was a significant prolongation of the
PR interval. The T wave was inverted in leads I, II and III in 3,
inverted in leads II and III in 2, flat in all three leads in 1, flat in
lead I and inverted in leads II and III in 1 and flat in lead II and
inverted in lead III in 2. The PR interval was prolonged in 2 patients
whose T waves were abnormal.

The electrocardiograms obtained in cases 1, 3, 7, 9 and 13, accompanied with a brief clinical description, are illustrated (figs. 1, 2, 3, 4 and 5).

Electrocardiograms were obtained as early as nine days after the onset of the acute streptococcic illness of the respiratory tract for 10 of the patients. Abnormalities that persisted for three to more than twenty-eight days were discovered in 8 on the first examination. All but 1 of these patients had been afebrile for three to six days at this time.
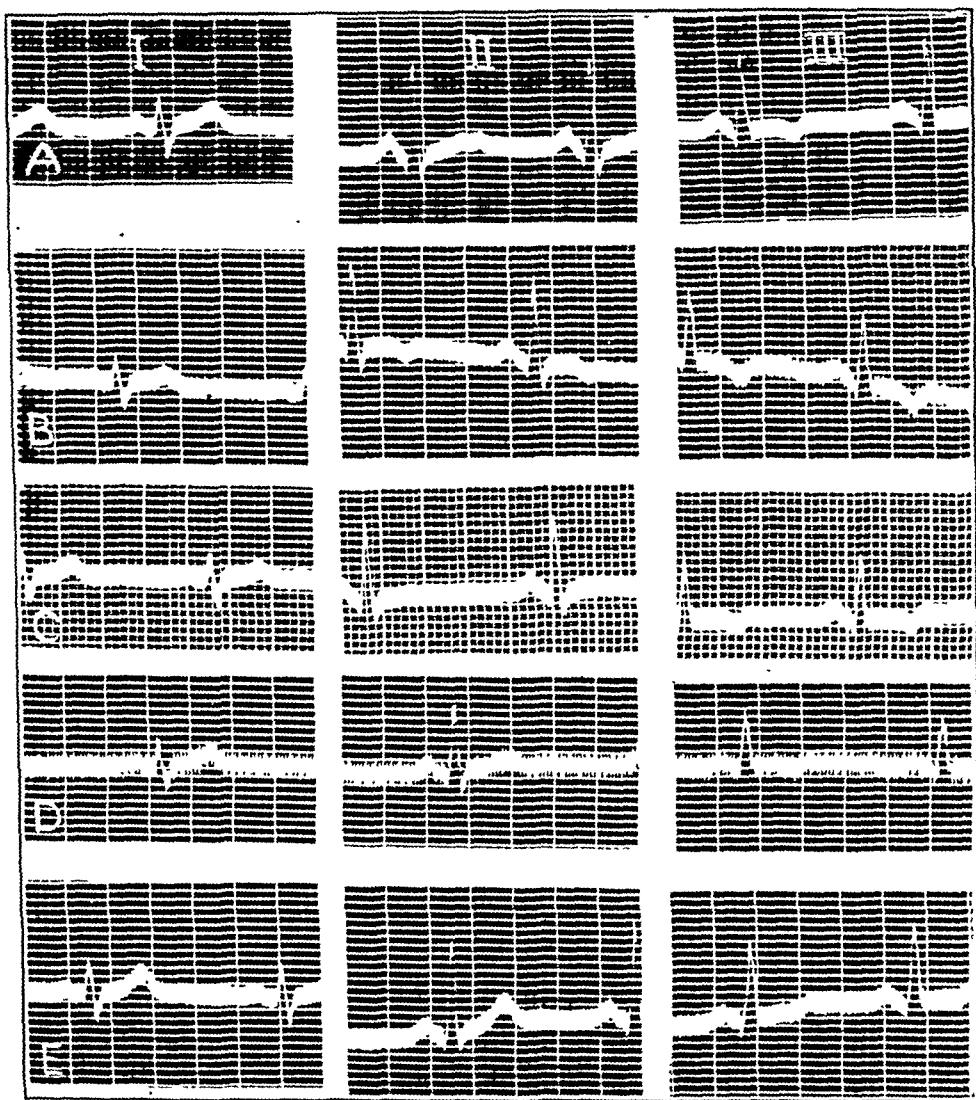

Fig. 3 (case 7).—Nonarthritic continuing disease. There were progressive changes in the T waves from the ninth day, with a return to normal. There was partial flattening in lead I and inversion in leads II and III. *A*, the ninth day, with the erythrocyte sedimentation rate 68 mm. per hour. *B*, the fourteenth day, with the erythrocyte sedimentation rate 48 mm. per hour. *C*, the eighteenth day, with the erythrocyte sedimentation rate 20 mm. per hour. *D*, the twenty-third day, with the erythrocyte sedimentation rate 15 mm. per hour. *E*, the thirty-fourth day, with the erythrocyte sedimentation rate 25 mm. per hour.

Nine additional patients were studied for the first time on the tenth to fourteenth days, and the initial electrocardiograms were abnormal for 6.

Insufficient serial examinations were performed to determine the precise duration of the electrocardiographic abnormalities. They were observed to persist for seven or more days in 15 patients, for fourteen or more days in 9, for twenty or more days in 7 and for twenty-eight or more days in 3.

That a continuing tissue reaction was established in these patients is further emphasized by the duration of abnormal erythrocyte sedimentation rates (more than 20 mm. per hour) that were present for fourteen days in 21, for twenty days in 16, for thirty days in 13, for 40 days in 8 and for fifty or more days in 1.
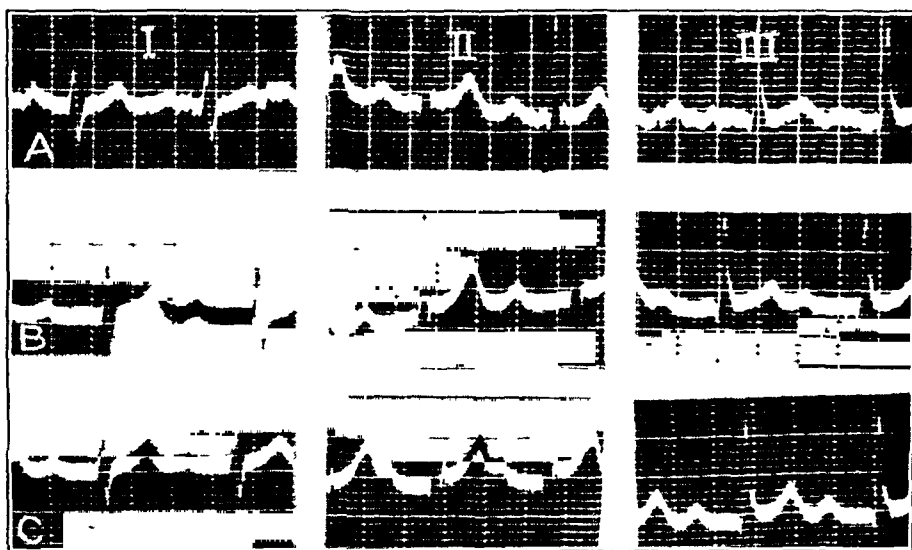

Fig. 4 (case 9).—Nonarthritic continuing disease. There was definite prolongation of the PR interval. *A*, the twenty-fourth day, the fifth day of the first bout of poststreptococcic fever, with the erythrocyte sedimentation rate 50 mm. per houi. *B*, the thirty-first day, the second day of the second bout of poststreptococcic fever, with the erythrocyte sedimentation rate 22 mm. per hour. *C*, the forty-second day, with the erythrocyte sedimentation rate 20 mm. per hour; the patient was afrebile and working.

Arthritic Continuing Disease.—Nine patients with poststreptococcic arthritic continuing disease (rheumatic fever) were observed for whom abnormalities in the electrocardiogram were discovered. No evidence of carditis was present in 7 similar patients.

The abnormalities were similar to those just described. The T waves were flat or inverted in 4, in 2 of which there was also exhibited prolongation of the PR interval. A conduction defect was demonstrated in the other 5 patients which was somewhat more marked than that usually present in the nonarthritic disease. Complete heart block occurred once.

Arthritic poststreptococcic disease was more severe than the non-arthritic type, as indicated by the more prolonged duration of abnormalities in the electrocardiogram and in the erythrocyte sedimentation rate, but it must be emphasized that there was overlapping between the two groups in this respect.

Electrocardiograms were obtained in 4 cases five, six, twenty-seven and sixty days before the onset of arthritis, and abnormalities were discovered in each on the first examination.

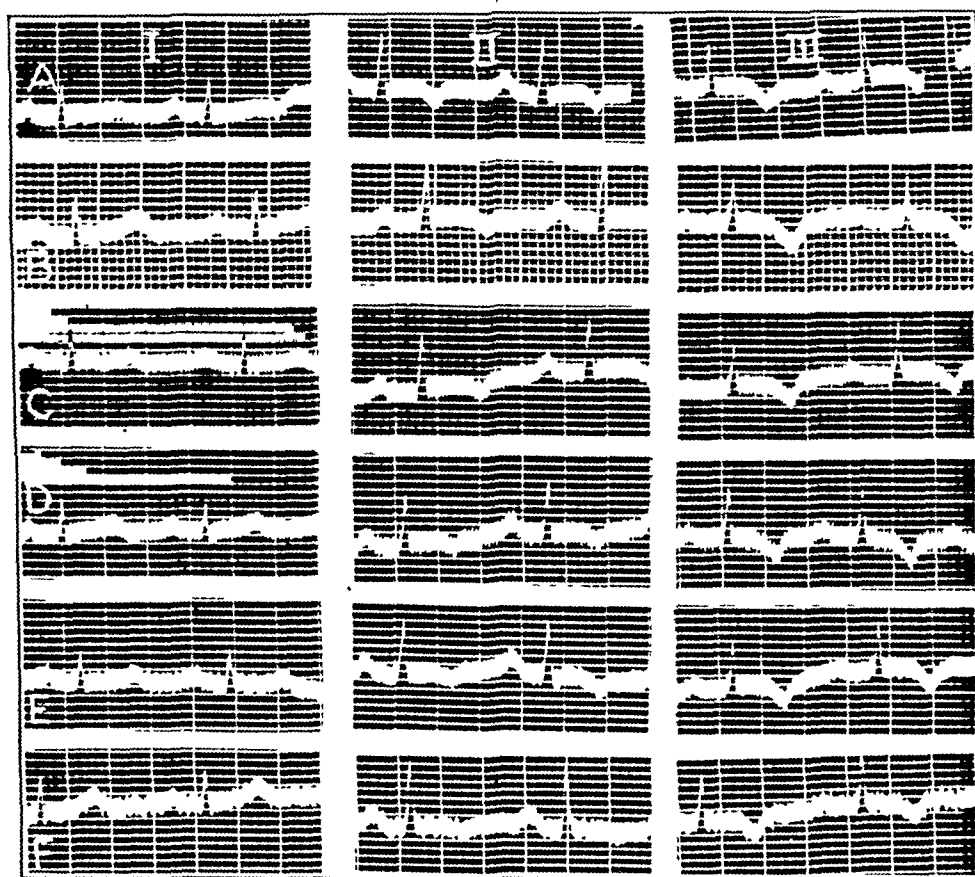Cases 24, 26 and 28 are illustrated and described (figs. 6, 7 and 8).

Fig. 5 (case 13).—Nonarthritic continuing disease. There was prolongation of the PR interval and progressive changes in the T waves. There was flattening in lead I and inversion in leads II and III. The conduction time returned to normal, but the T waves did not. *A*, the ninth day, with the erythrocyte sedimentation rate 50 mm. per hour; the patient was febrile. *B*, the fourteenth day, with the erythrocyte sedimentation rate 30 mm. per hour; the patient had been afrebile for twenty-four hours. *C*, the nineteenth day, with the erythrocyte sedimentation rate 44 mm. per hour. *D*, the twenty-fourth day, with the erythrocyte sedimentation rate 35 mm. per hour. *E*, the twenty-eighth day, with the erythrocyte sedimentation rate 28 mm. per hour. *F*, the thirty-third day, with the erythrocyte sedimentation rate 6 mm. per hour.

COMMENT

This study has revealed that definite electrocardiographic evidence of carditis may be demonstrated in many persons who have undergone an acute group A hemolytic streptococcic infection of the respiratory

tract. Prolongation of the PR interval or abnormalities in the T waves or both were discovered.

The presence of carditis was invariably associated with other evidence of a continuing abnormal tissue reaction. In some cases an elevated erythrocyte sedimentation rate was the only sign of an active process; in others, fever and malaise were present, and
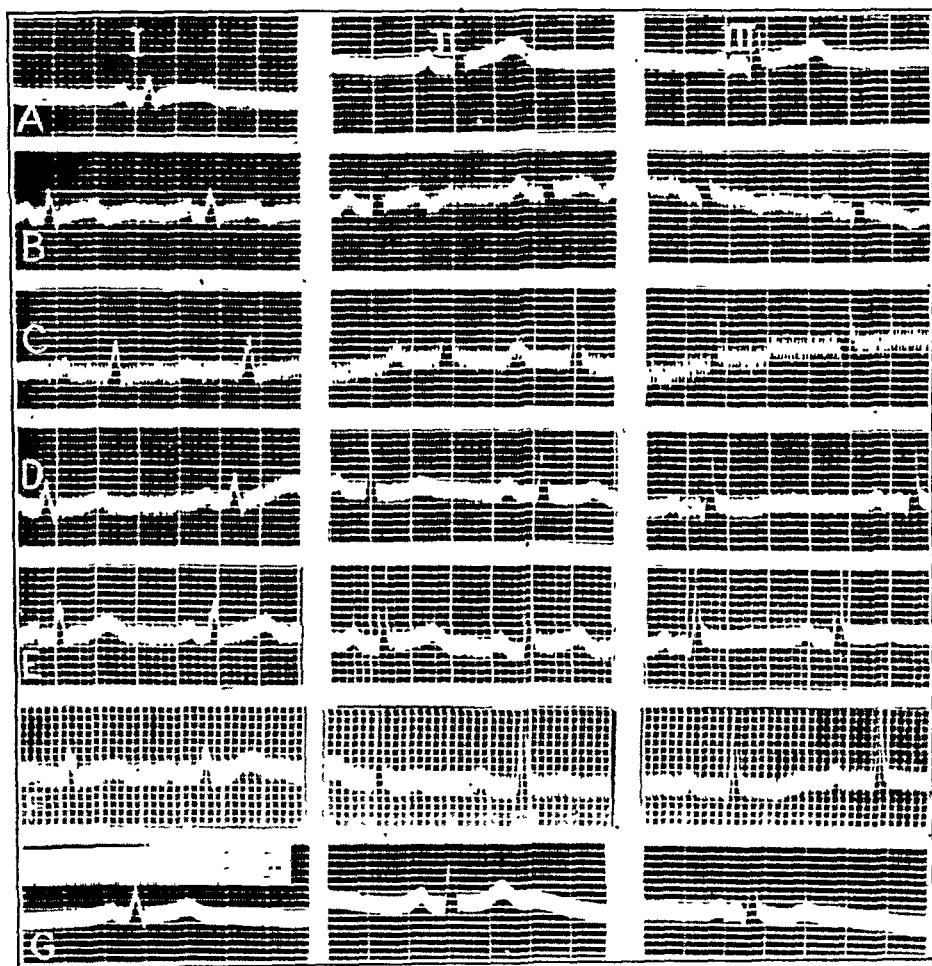

Fig. 6 (case 24).—Nonarthritic continuing disease followed by development of arthritis. *A*, the tenth day, with the erythrocyte sedimentation rate 50 mm. per hour and the electrocardiogram normal. *B*, the twenty-third day, with the erythrocyte sedimentation rate 89 mm. per hour, marking the onset of nonarthritic poststreptococcic fever. The T waves were inverted in all leads. *C*, the twenty-eighth day, with the erythrocyte sedimentation rate 107 mm. per hour, the sixth day of the poststreptococcic fever. The PR interval was 0.32 seconds. *D*, the thirty-fourth day, with the erythrocyte sedimentation rate 85 mm. per hour. The patient had been afrebile for four days. There was a slight flattening of the T waves in all leads. *E*, the forty-seventh day, with the erythrocyte sedimentation rate 65 mm. per hour. The electrocardiogram was approximately normal. *F*, the ninetieth day, with the erythrocyte sedimentation rate 35 mm. per hour, eight days after the onset of arthritis. The PR interval was 0.22 seconds. *G*, the one hundred and eighteenth day, with the erythrocyte sedimentation rate 15 mm. per hour and the electrocardiogram normal.

in a few arthritis also appeared. When arthritis was present, the clinical syndrome was similar in every respect to that associated with typical rheumatic fever. The illness was frequently prolonged, and this was more often the case if the joints were involved. There was, however, much overlapping, both in severity and duration, and it seems quite impossible to establish adequate criteria for the sharp differentiation between arthritic and nonarthritic nonsuppurative poststreptococcic continuing disease. The fact that carditis was present soon after the acute illness of the respiratory tract had subsided and days to weeks
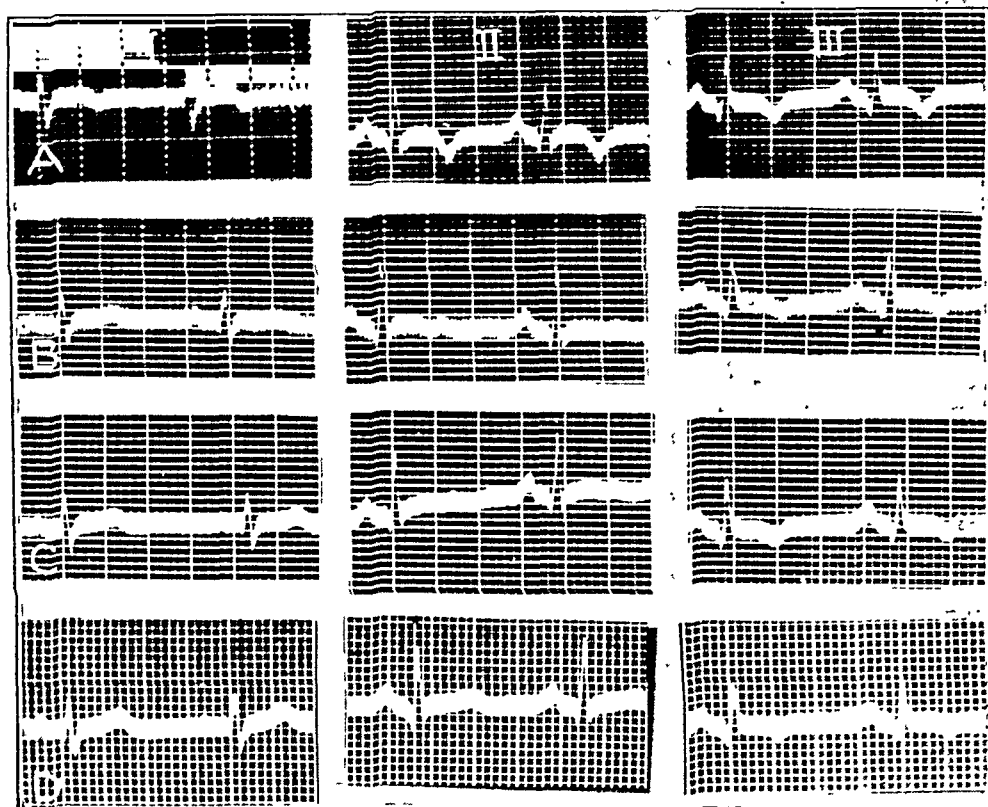

Fig. 7 (case 26).—Nonarthritic continuing disease followed by the development of arthritis. *A*, the thirty-sixth day, with the erythrocyte sedimentation rate 38 mm. per hour, twenty-seven days before the onset of arthritis. The T waves were inverted in leads I, II and III. *B*, the seventy-third day, with the erythrocyte sedimentation rate 80 mm. per hour, ten days after the onset of arthritis. The T waves were returning to normal. *C*, the eightieth day, with the erythrocyte sedimentation rate 50 mm. per hour. The T waves were more nearly normal. ·*D*, the one hundred and eighth day, with the erythrocyte sedimentation rate 15 mm. per hour. The T waves were approximately normal.

before articular involvement was manifest is of importance. Various aspects of this subject have been discussed in detail elsewhere.[1]

It is necessary for the purpose of this report only to determine whether the described electrocardiographic abnormalities are unique to the poststreptococcic state and if they are similar to those previously observed in rheumatic fever. Several reports are available that

describe the relatively frequent occurrence of electrocardiographic abnormalities following a hemolytic streptococcus disease of the respiratory tract, usually scarlet fever. Roelsen,[2] in an extensive survey, discovered both changes in the T wave, which were more likely to occur early, and prolongation of the PR interval. The latter, abnor-
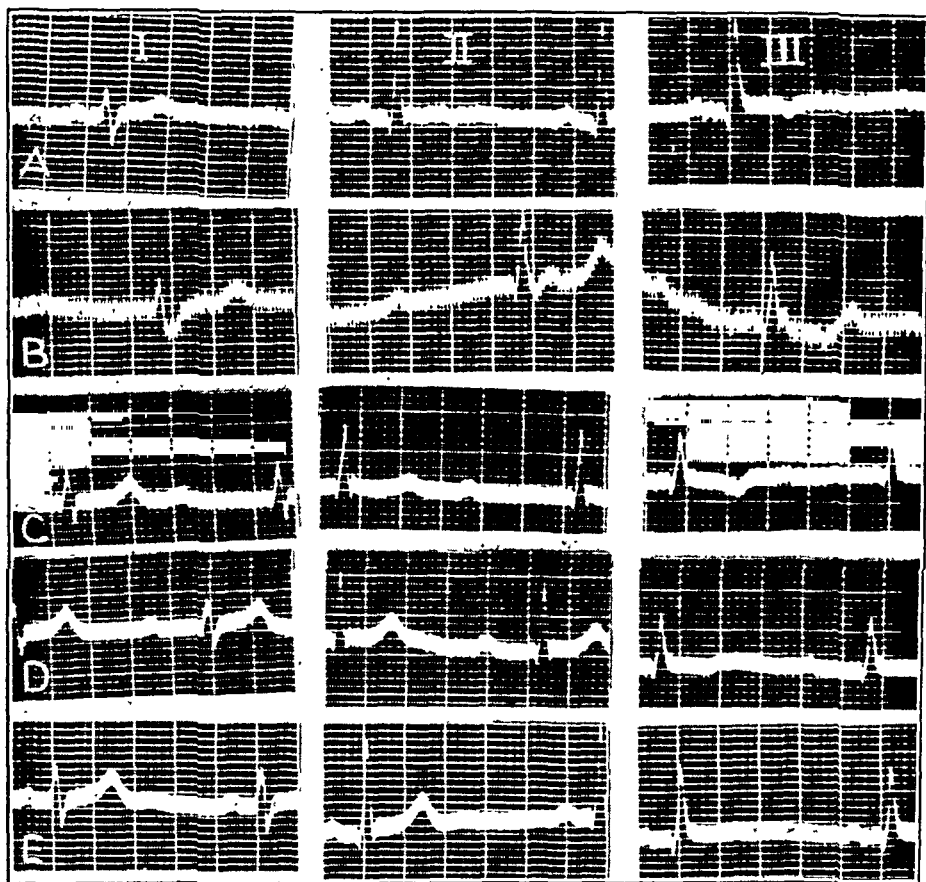

Fig. 8 (case 28).—Arthritic continuing disease. *A*, the seventh day, with the erythrocyte sedimentation rate 30 mm. per hour, five days before the onset of poststreptococcic fever. The T waves were flat or inverted in all leads. *B*, the nineteenth day, with the erythrocyte sedimentation rate 90 mm. per hour, seven days after the onset of poststreptococcic fever and the first day of arthritis, which was minimal. Complete heart block was present. *C*, the twenty-seventh day, with the erythrocyte sedimentation rate 50 mm. per hour, the PR interval greatly prolonged and the T waves returning to normal. *D*, the twenty-ninth day, with the erythrocyte sedimentation rate 50 mm. per hour, the PR interval shortening and the T waves about normal. *E*, the ninetieth day, with the erythrocyte sedimentation rate 10 mm. per hour and the electrocardiogram normal.

mality was more frequently observed and was more pronounced in arthritic patients. The observations of Faulkner, Place and Ohler[3]

2. Roelsen, E.: Electrocardiographic Studies in Scarlet Fever, Acta med. Scandinav. **106**:26, 1941.

3. Faulkner, J. M.; Place, E. H., and Ohler, W. R.: The Effect of Scarlet Fever on the Heart, Am. J. M. Sc. **189**:352, 1935.

were similar, except that all the electrocardiograms obtained before the thirteenth day of the acute disease of the respiratory tract were normal. This result was in striking contrast with the results of this study.

Descriptions of electrocardiograms obtained during and after the course of other acute infectious diseases are few and incomplete, Master, Romanoff and Jaffe [4] described conduction defects and changes in the T wave in a significant percentage of all cases of typhoid, typhus, gonococcic arthritis, pulmonary tuberculosis, malaria, rheumatoid arthritis and lobar pneumonia. Only in connection with the last disease was the natural history of the electrocardiographic abnormalities described in detail. Definite changes in the T wave were present only during the acute febrile phase of the illness. The PR interval was greater than 0.20 second in 11 per cent of all cases. In this small group the abnormality appeared late in the course of the disease and persisted throughout convalescence.

A few other papers [5] described abnormal electrocardiograms following "influenza." In the absence of more definite information, it is possible that this disease was actually hemolytic streptococcus infection of the respiratory tract. Bang [6] has stated that conduction defects may occur in association with gonorrheal arthritis.

Electrocardiographic abnormalities essentially similar to those described in this paper have been observed recently following epidemic parotitis (mumps).[7] The changes were present early in the illness and were transitory, persisting for only four to eight days in most instances.

The available information indicates that abnormalities of the electrocardiogram of the type that were discovered during the poststreptococcic state may also be observed during and after attacks of other infectious diseases. Definite statements are not available which permit an evaluation of the circumstances under which they may occur in relation to nonstreptococcic infections. It seems probable that the frequency, duration and magnitude of the abnormalities will be greater after an infection by hemolytic streptococci, but true specificity of the observed changes cannot be established.

4. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, Proc. Soc. Exper. Biol. & Med. **31**:931, 1934. Master, A. M.; Romanoff, A., and Jaffe, H.: Electrocardiographic Changes in Pneumonia, Am. Heart J. **6**:696, 1931.

5. Burnett, C. T., and Piltz, G. F.: The Electrocardiogram in the Acute Infections, J. A. M. A. **93**:1120 (Oct. 12) 1929. Hyman, A. S.: Post-Influenzal Heart Block, M. J. & Rec. **124**:698, 1926.

6. Bang, O.: Gonorrheal Myocarditis, Brit. M. J. **1**:117, 1940.

7. Rosenberg, D. H.: Electrocardiographic Changes in Epidemic Parotitis (Mumps), Proc. Soc. Exper. Biol. & Med. **58**:9, 1945.

Few comprehensive studies of the electrocardiogram in connection with acute rheumatic fever have been published. Prolongation of the PR interval,[8] heart block,[9] "coronary type" T waves [10] and variations in the QRST segment with pericarditis [11] have been described. It is common knowledge that all these variations from the normal may occur, but precisely how frequently, to what degree and in what combination could not be ascertained.

In Wilson's group of 54 cases,[12] prolongation of the PR interval was most commonly observed, but changes in the T wave also occurred. Pardee [13] stated: "If frequent records are taken during the acute stage of this disease (rheumatic fever) more than 60 per cent of cases will be found to show inversion or other abnormalities of the T wave such as have been described as resulting from myocardial disease. A large number will show variations in the duration of the auriculoventricular conduction time . . . Many will show both of these types of electrocardiographic change."

It is proper to conclude that the abnormalities of the electrocardiogram observed during this study of the nonsuppurative complications of acute hemolytic streptococcus infection of the respiratory tract were similar to those usually associated with rheumatic fever. This evidence adds weight to the conclusion that poststreptococcic continuing disease with arthritis was a tissue reaction identical with that ordinarily described as rheumatic fever and that the nonarthritic illness was a closely related process.

SUMMARY

A nonsuppurative continuing disease, often associated with abnormalities of the electrocardiogram, commonly follows acute group A hemolytic streptococcus disease of the respiratory tract. Arthritis may or may not accompany this process.

Prolongation of the PR interval and flattening and inversion of the T waves were observed.

8. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1, 1924.

9. Wedd, A. M.: Complete Heart Block in Rheumatic Fever, Am. Heart J. **14**:759, 1937.

10. Porte, D., and Pardee, H. E. B.: The Occurrence of the Coronary T Wave in Rheumatic Pericarditis, Am. Heart J. **4**:584, 1929.

11. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis, Arch. Int. Med. **61**:381 (March) 1938.

12. Wilson, M. G.: Rheumatic Fever, New York, Commonwealth Fund, 1940.

13. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, Inc., 1941.

The changes in the electrocardiogram were similar in nonarthritic and in arthritic cases, but they were more definite and persisted for longer periods if the joints were involved.

The observed electrocardiographic abnormalities are not unique to the poststreptococcic state but are identical with those previously discovered during the course of acute rheumatic fever.

Progress in Internal Medicine

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INFECTIOUS MONONUCLEOSIS

AN increasing number of papers are appearing in the literature dealing with infectious mononucleosis, which is a malady of unusual interest chiefly because of its tendency to simulate so many other disease syndromes with its diverse symptoms, because there is still considerable doubt concerning its causation and its pathologic changes and because of the unique presence of sheep cell agglutinins in the blood of patients with this disease.

Attempts have been made by Julianelle, Bierbaum and Moore [215] to transmit infectious mononucleosis to rabbits and monkeys and, to a lesser extent, to white mice, guinea pigs and human beings. Specimens of blood were withdrawn from 15 patients during the febrile stage, on the second to the seventh day after the onset, except in 1 instance in which the collection was made on the tenth day of illness, after two days of normal temperature. Experiments were controlled with blood from 3 patients with streptococcic septicemia and pneumonitis of unknown cause and Rocky Mountain spotted fever. An effort was also made to transmit the disease with washings obtained by gargling with 25 to 50 cc. of isotonic solution of sodium chloride before breakfast. Four of these experiments were carried out, in which 16 rabbits and 4 monkeys were employed. Three experiments were done with excised tissue from the lymph nodes in an attempt to transmit the disease to monkeys and rabbits. In addition, the material from 2 other lymph nodes prepared in a similar manner was given to 2 healthy human

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215. Julianelle, L. A.; Bierbaum, O. S., and Moore, C. V.: Studies on Infectious Mononucleosis, Ann. Int. Med. **20**:281, 1944.

volunteers, neither of whom had any knowledge of having previously had infectious mononucleosis. In brief, it was found that a distinct tendency toward leukocytosis, with increases in both lymphocytes and monocytes, occurred in the animals but that in no case did the leukocytes present the characteristics of those seen in patients with infectious mononucleosis. Furthermore, the controlled observations indicated strongly that the changes in the blood were a nonspecific response possibly to foreign proteins. There were no cytologic changes observed in any of the 4 human volunteers who served as subjects for experiments. Furthermore, there was no evidence to indicate the development of heterophile antibodies in any of the animals, as only a relatively small proportion showed a low and transitory increase in titer. Attempts to demonstrate the virus by propagation in eggs led to the conclusion that either it was not present in the material employed or this medium does not support its growth. Attempts to transmit the disease to human beings were unsuccessful. Two subjects gargled with throat washings from 1 patient, and 2 others permitted the intramuscular injection of a saline extract from cervical lymph nodes removed from patients during the febrile period of the disease. Also, 1 of these 2 subjects sprayed the nasopharynx with a portion of the saline extract. In no instance did hematologic changes result which indicated that transmission had occurred. Although previous reports indicate that infectious mononucleosis may be due to a filterable virus, there is nothing in these experiments, which seem to have been carried out rather carefully, to substantiate this theory. There is apparently, therefore, an inconsistency between the results reported in the literature and of these experiments which further investigation alone can resolve.

One of the few fatal cases of infectious mononucleosis in which there has been a careful pathologic examination of the tissues is reported by Ziegler.[216] The patient was a 22 year old white woman who suddenly died, after an illness of between three and four weeks, in a state of severe shock as the result of spontaneous rupture of the spleen. There are now on record 3 cases of ruptured spleen resulting from this disease, and of the 3 patients 1 died and the other 2 were saved by surgical intervention. The pathologic study indicates that infectious mononucleosis is an acute or subacute infectious disease of unknown cause, having many diverse clinical and pathologic manifestations. The essential pathologic lesions of infectious mononucleosis are focal lesions in the various organs of the body, especially the liver, kidneys, lymph nodes and spleen. Ziegler regards it as a generalized infection with specific localization in one or more of the tissues or

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216. Ziegler, E. E.: Infectious Mononucleosis: Report of Fatal Case with Autopsy, Arch. Path. **37**:196 (March) 1944.

organs of the body. Various lesions have formerly been described in the lymph nodes, the spleen, the tonsils and the marrow. To these have been added the changes in the liver, the kidneys, the spleen and the lungs of the patient reported by Ziegler. According to this observer, the monocytes cannot be distinguished in tissue sections from the peculiar large lymphocytes as readily as in stained blood smears. In addition, the lesions, especially those in the spleen, contain large cells which one might classify as lymphoblasts, clasmatocytes or stem cells. The edema, the cloudy swelling and the infiltrative changes found in the liver and the spleen explain the enlargement of these organs. The jaundice, which occurs not uncommonly, may be explained on the basis of profuse focal hepatitis, which is a somewhat better hypothesis than that of swelling of the lymph nodes in the region of the bile duct, at least in those cases in which the enlarged liver is present. Although Ziegler did not obtain nerve tissue for study, he states that one could readily imagine full-sized mononuclear infiltration in the central nervous system or perhaps merely edema and obstruction of capillaries, such as he demonstrated in the lung, as the basis for neurologic manifestations.

A 33 year old man with infectious mononucleosis whose spleen spontaneously ruptured is reported on by Darley, Black, Smith and Good. [217] It is of special interest that pathologic studies of the spleen were made and reported. This patient had the characteristic clinical signs of infectious mononucleosis with two interesting features—he was jaundiced and had severe abdominal pain requiring morphine for relief. On the sixteenth day of the illness the patient was awakened from sleep suddenly by a stabbing agonizing pain in the midepigastrium and back. He went into a state of shock almost immediately. Laparotomy revealed a large tear near the hilus of the spleen which necessitated splenectomy. Convalescence was satisfactory, and the patient was discharged from the hospital on the twelfth postoperative day. The spleen weighed 460 Gm. and measured 14.5 by 10 by 6 cm. A ragged tear measuring 4 cm. in length was present on the anterior margin. Microscopic examination showed that the red pulp was crowded with lymphoid cells of all types which tended to obscure the sinusoidal structures, but evidence of proliferation of these cells *in situ* was not seen. Proliferative activity of clasmatocytes on a large scale was not demonstrable. Large lymphoid cells corresponding to those described as "infectious mononucleosis cells" were fairly numerous in both the sinusoids and the pulp spaces. As far as we are aware, this is the third case of rupture of the spleen in the course of infectious mono-

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217. Darley, W.; Black, W. C.; Smith, C., and Good, F. A.: Spontaneous Splenic Rupture in Infectious Mononucleosis: A Case and Pathologic Report, Am. J. M. Sc. **208**:381, 1944.

nucleosis which has been reported in the literature. A similar case was reported by King.[218]

One of the best reviews dealing with infectious mononucleosis in recent years has been written by Contratto.[219] Careful consideration has been given to a study of 196 cases of this disease in patients admitted to the Stillman Infirmary, connected with Harvard University. Reference has been made to the incidence, symptoms, physical signs, changes in the blood, heterophile test, complications, length of hospitalization, recurrences and relapses and therapy. No attempt will be made to give his conclusions in detail, but the reader who is interested in this subject is advised to give the article a careful perusal. He states that infectious mononucleosis is a benign illness, but it should be noted that elsewhere in this review there is 1 case reported of a fatality due to a spontaneously ruptured spleen. We are in accord with Contratto's statement that an accurate clinical diagnosis may be difficult on account of the variability of symptoms and other manifestations. The major problem in this disease is the making of a differential diagnosis, which can be accomplished by heterophile test and blood cell study. We are not in entire accord with his view, however, that this can always be done "easily," because it is our belief that the recognition of the atypical lymphocytes which are so characteristic of the disease requires considerable experience. He emphasizes the importance of making frequent heterophile tests and hematologic examinations for the presence of atypical lymphocytes during the course of the disease, since in infectious mononucleosis there is often a delay of days or even several weeks before the hematologic changes are conclusive enough to permit an accurate diagnosis.

Infectious mononucleosis is divided into four types by Etcheverry [220] as follows: the glandular, the pharyngeal, the febrile and the icteric. He comments that the last is less common and less known. The icteric type is divided into three groups, in one of which the diagnosis is made, only by the presence of atypical leukocytes in the peripheral blood and a positive Paul-Bunnell reaction. In such cases, no other evidence of infectious mononucleosis may be present except the jaundice. He emphasizes that in some cases there may be a splenomegaly which sometimes persists for as long as five to seven years and perhaps longer. It is important to note that in a case of lymphocytic leukemia the Paul-Bunnell reaction was positive with a dilution of 1 : 896. The author thought that this possibly might be attributed to the repeated

218. King, R. B.: Spontaneous Rupture of the Spleen in Infectious Mononucleosis: Report of Case, New England J. Med. **224**:1058, 1941.

219. Contratto, A. W.: Infectious Mononucleosis: Study of 196 Cases. Arch. Int. Med. **73**:449 (June) 1944.

220. Etcheverry, M. A.: Mononucleosis infecciosa, Dia méd. **16**:697, 1944.

injections of liver extract received by the patient. The product injected was made from sheep livers, and the possibility arises that it might contain the antigen responsible for the reaction. According to him, the Widal reaction may occasionally be positive in infectious mononucleosis.

The various clinical forms of infectious mononucleosis are discussed by Leunda.[221] According to him they may be divided into the typical and more usual types, such as glandular and anginose, and the atypical forms, which are the febrile, the rhinopharyngeal, the pulmonary and the nervous.

Comprehensive reviews of the literature bearing on infectious mononucleosis are given by Taillens [222] and by Stolinsky.[223]

Immerman [224] reports observations during an epidemic, in which he observed 200 cases of infectious mononucleosis. It is emphasized that the disease may be symptomatic or atypical and continue so for weeks or months. During this time, depression of the polymorphonuclear cells and the appearance of abnormal lymphocytes constitute the easiest clues to the diagnosis. In his experience the abnormal blood picture may continue for six months and perhaps for months longer. He calls attention to the paper by Randolph and Gibson,[225] mentioned in this review, in which they report that 24 patients with allergic conditions had typical cells of infectious mononucleosis in the blood in the percentage of 10 to 20 and negative heterophile reactions. He states that he now has 6 patients with angina pectoris with or without coronary thrombosis who also have these same cells; hence he argues that angina pectoris may cause the appearance of cells typical of infectious mononucleosis. He thus infers that the occurrence of these cells in any given pathologic condition does not necessarily indicate an etiologic relation.

It is stated by Beck [226] that Fennel, in December 1934, reported the first 4 proved cases of infectious mononucleosis to occur in Hawaii, with a case of probable infectious mononucleosis occurring in the previous

221. Leunda, J. J.: Formas clínicas de la mononucleosis infecciosa, Rev. argent.-norteam. cien. méd. **1**:381, 1943.

222. Taillens, J. P.: La maladie de Pfeiffer (angine à monocytes, mononucléose infectieuse, fièvre ganglionnaire), Schweiz. med. Wchnschr. **73**:267, 1943.

223. Stolinsky, A.: Infectious Mononucleosis: A Summary of the Literature with a Case Report, M. Rec. **157**:483, 1944.

224. Immerman, S. L.: An Epidemic of, Infectious Mononucleosis, with a Report of Two Hundred Cases, M. Rec. **157**:480, 1944.

225. Randolph, T. G., and Gibson, E. B.: Blood Studies in Allergy: The Presence in Allergic Disease of Atypical Lymphocytes and Symptoms Suggesting the Recovery Phase of Infectious Mononucleosis, Am. J. M. Sc. **207**:638, 1944.

226. Beck, L. C.: .Infectious Mononucleosis, Proc. Staff Meet. Clin., Honolulu **10**:53, 1944.

year in a soldier who had recently come to Hawaii. We must emphasize, however, that the disease undoubtedly was present before this time, if for no other reason than that American soldiers occupied the island of Hawaii for a good many years prior to 1934 and that it is inconceivable that the condition had not been carried to the island by persons with unrecognized disease. He points out the characteristic clinical manifestations and warns that a mild epidemic of infectious mononucleosis appeared imminent when this paper was published, in 1944. It seems likely that this might easily occur with the large number of American troops on the island.

Seven cases of infectious mononucleosis were observed during a period of four months in such widely separated places in Tanganyika Territory [227] that it would appear that the cases were sporadic and not part of an epidemic. The author deduces that since all 6 patients seen by him personally had a mild infection of the fauces the condition might be conveyed by droplet infection. While this mode of transmission is a possibility, certainly his cases afford no conclusive proof of it. He makes one interesting observation to the effect that he himself was the patient in case 2 and he first examined the patient in case 1 nine days before he began to have the symptoms of the disease. He states that in no other instance was he able to find the source of the infection or any information concerning the incubation period.

An epidemic in which 123 cases of infectious mononucleosis were observed is reported by Stevenson and Brown.[228] Hematologic changes highly suggestive of the condition were the most constant finding, as 110 of the 123 patients had a "mononuclear reaction." Some patients with infectious mononucleosis were admitted to the hospital with conditions which were thought to have had no bearing on this syndrome, such as fractures and associated Vincent infection of the mouth. One patient had a laparotomy performed for symptoms in the lower part of the abdomen which we assume were due to the characteristic abdominal pain due to infectious mononucleosis. This patient had demonstrable antibodies in her blood in a dilution of 1 : 224 the day after her admission to the hospital, and there was no appreciable alteration in the titer in the following few weeks. Glandular involvement was present in a great majority of cases. The authors had the clinical impression that the infection manifests itself differently in different hosts and may lead to erroneous diagnosis. The appearance of an apparently seronegative form of the disease occurred more frequently than was anticipated. In their opinion infectivity was not established in this limited study.

227. Reed, H.: An Outbreak of Infective Mononucleosis in Tanganyika, J. Trop. Med. **47**:42, 1944.

228. Stevenson, E. M. K., and Brown, T. G.: Infectious Mononucleosis: Preliminary Investigation of Series of Cases, Glasgow M. J. **140**:139, 1943.

Two cases of infectious mononucleosis in Negro children are reported by Johnson.[229] The author states that as far as he knows these are the first serologically proved cases of its occurrence in Negroes in the literature. He refers to a previous case in a Negro man which was reported by Longcope.[230] Johnson states that no explanation can be offered for the apparent rarity of this disease on a racial basis. Three cases of infectious mononucleosis in Negroes are reported by Ray and Cecil.[231] These comprise 12 per cent of the cases of this disease observed in the Medical College of Virginia Hospital over a period of five years. The prompt improvement which was noted in 1 patient following the administration of sulfadiazine they attribute to the control of secondary invaders. It is of interest to note that in 1 case the disease was complicated by the presence of sickle cell anemia.

It is emphasized by Mitchell and Zetzel [232] that infectious mononucleosis is a protean disease second only to syphilis in its ability to mimic other conditions. They state that in the army hospital with which they were associated the diagnosis of infectious mononucleosis was made only twice in the years 1941 and 1942. It should be noted, however, that during the year 1943, when the medical personnel became interested in the complexity of the manifestations of infectious mononucleosis, the diagnosis was confirmed in 23 additional cases. This experience is in accord with our opinion that the diagnosis of infectious mononucleosis is much more frequently overlooked than it is made. It is interesting to note that the disease was recognized in only 8 of the 34 patients at the time of admission to the hospital. The incorrect preliminary diagnoses most commonly made were nasopharyngitis, cervical adenitis, catarrhal jaundice and sinusitis. The authors emphasize correctly the fact that patients with this disease have a prolonged convalescence with persistent headache and asthenia and in some instances the diagnosis of psychoneurosis may be made unjustly. They advise that the use of the convalescent and reconditioning section of the Army Medical Corps may shorten the patient's stay in the hospital and hasten his return to active duty.

The importance of the differentiation between infectious mononucleosis and brucellosis has been emphasized by Rubenstein and Shaw.[233]

229. Johnson, R. D.: Infectious Mononucleosis in the Negro: Report of Two Cases in Children, J. A. M. A. **124**:1254 (April 29) 1944.

230. Longcope, W. T.: Infectious Mononucleosis, Am. J. M. Sc. **164**:781, 1922.

231. Ray, E. S., and Cecil, R. C.: Infectious Mononucleosis in Negro: Report of Three Cases, with One Complicated by Sickle Cell Anemia, South. M. J. **37**:543, 1944.

232. Mitchell, R. H., and Zetzel, L.: Infectious Mononucleosis in Army, War Med. **5**:356 (June) 1944.

Among a number of possibilities, one should keep in mind both of these diseases when fever of undetermined origin is the outstanding feature of the clinical course. This problem was approached by examining for the presence of sheep cell agglutinins characteristic of infectious mononucleosis all blood specimens sent in for agglutination tests for brucellosis to the Laboratory of the Division of Communicable Diseases, Massachusetts Department of Public Health. Both tests were performed on a series of 1,000 consecutive specimens of blood serum submitted to the laboratory. In each serum in which a positive sheep cell agglutination was elicited. the physician was interviewed to obtain additional clinical and laboratory data. When the titer was less than 1:128, a second specimen was requested to ascertain the titer later in the course of the disease. They found 13 positive agglutinations of sheep cells in 1,000 specimens for testing. In only 2 of these 13 cases had the diagnosis of infectious mononucleosis been suspected. It should be pointed out, however, that in many of the patients there had been symptoms of long duration. Since infectious mononucleosis is usually an acute, comparatively brief febrile illness, it is scarcely to be expected that positive heterophile reactions would be found in the patients with long-standing symptoms. If these chronic infections had been excluded, undoubtedly the percentage of cases of infectious mononucleosis would have been appreciably greater. This study serves to remind one that in all patients with acute febrile diseases of obscure origin, the possibility that either brucellosis or infectious mononucleosis might be present should be given serious attention.

The important fact is pointed out by Lloyd[234] that purpuric phenomena, even with decided reduction of platelets, may occur in a patient with infectious mononucleosis. Purpura does not necessarily constitute an absolutely infallible diagnostic point in favor of leukemia. His patient was a youth aged 20, who had the symptoms of an infection of the upper respiratory tract and, in addition, had a characteristic lymphocytosis. with numerous large lymphocytes and atypical mononuclear forms, combined with a heterophile agglutination of 1:512. These findings were thought to be sufficient to make a positive diagnosis of infectious mononucleosis despite the absence of significant lymphadenopathy and a palpable spleen. Platelets numbered as low as 66,000 per cubic millimeter. There was no significant anemia, and the highest white blood cell count was 20,300 per cubic millimeter. Judging from this case, it is pointed out by Lloyd that severe infectious mononucleosis may be indistinguishable in its early stages from acute lymphatic leukemia, even though the

233. Rubenstein, A. D., and Shaw, C. I.: Infectious Mononucleosis Simulating Brucellosis, New England J. Med. 231:111, 1944.

234. Lloyd, P. C.: Acute Thrombocytopenic Purpura in Infectious Mononucleosis: Report of Case, Am. J. M. Sc. 207:620, 1944.

presence of purpura has long been considered an important diagnostic point in favor of the latter. In the light of the case at hand, however, he emphasizes that purpuric and hemorrhagic phenomena with or without thrombopenia cannot constitute a valid distinguishing feature between the two conditions. He does emphasize, however, that the finding of a well defined anemia is exceedingly rare in infectious mononucleosis and that if the condition is associated without obvious explanation one may well suspect the presence of a leukemic process. We wish to state two points in regard to Lloyd's case: (1) that purpura, although it may occur, is exceedingly rare in patients with infectious mononucleosis and is a valuable diagnostic point in differentiating acute leukemia from it and (2) that the possibility that purpura in a patient with infectious mononucleosis may be due to one of the sulfonamide drugs should always be investigated.

In an excellent review, Kaufman[235] states that he regards the heterophile antibody reaction as a laboratory procedure of considerable value in clinical medicine. He points out that one frequently speaks alternately of the Paul-Bunnell test and the sheep cell agglutination test and that in Europe the procedure is referred to as the Hanganatziu-Deicher reaction. He favors the Thompson modification of the David-sohn method, an account of which is soon to be published. It is accurate and simple and can be interpreted in one hour. In a study of 83 proved cases of infectious mononucleosis, he concludes that there are three aspects of the disease to be considered from the standpoint of diagnosis: the clinical, the hematologic and the serologic. If any two of them give positive evidence of the disease the diagnosis may be considered established. No cases in which there was a normal blood picture were observed to show positive clinical and serologic evidence of the disease. There were many cases, however, in which there was positive clinical and hematologic evidence of the disease but normal serologic reactions and a few cases in which there was positive hematologic and serologic evidence but a subclinical or an atypical clinical picture. It is concluded by Kaufman that when sheep cell agglutination occurs in a dilution of 1:32 with the Paul-Bunnell technic and in a dilution of 1:56 with the Davidsohn technic, it must be considered indicative of the disease. An agglutination in a dilution of 1:16 with the Paul-Bunnell technic and in a dilution of 1:28 with the Davidsohn technic requires further investigation. He believes that even repeatedly negative reactions do not by any means eliminate the diagnosis of infectious mononucleosis. Kaufman found that the reaction usually becomes positive between the sixth and twenty-sixth days of the illness and most commonly

235. Kaufman, R. E.: Heterophile Antibody Reaction in Infectious Mononucleosis, Ann. Int. Med. **21**:230, 1944.

between the twelfth and twenty-first days. It usually remains positive for two to four months after the onset, although this period varies greatly and it may return to negative much sooner or not until much later. Usually reactions which are positive in high titer will be found to persist longer periods of time. He cautions that a negative reaction does not rule out the diagnosis and that a positive one does not definitely establish it. In suspected cases the test should be repeated at intervals, and if the titer rises or if the reaction becomes positive after having been negative the diagnosis is established beyond doubt, provided the patient has not received an injection of horse serum a short time before. He has also found that an increased heterophile antibody reaction may occasionally follow the administration of serum or liver extract and may occur in cases in which the final diagnosis is something other than infectious mononucleosis, as, for example, in 1 case of Hodgkin's disease and in a case of rubella. He has no explanation of these false positive reactions.

It is stated by Randolph and Gibson [225] that in performing differential white blood cell counts for patients with allergic disease they frequently noted large mononuclear cells indistinguishable from the atypical lymphocytes seen in infectious mononucleosis. The question is immediately raised whether the patients in this series might not be convalescing from infectious mononucleosis. In only 1 case, however, was the heterophile antibody reaction positive. Seven of the patients in the remaining cases had been suspected of having had infectious mononucleosis in the past, but their heterophile antibody examinations had been consistently negative. It is pointed out that in the 24 allergic patients studied the symptoms of weakness, fatigue and lassitude, commonly observed also as sequelae to acute infectious mononucleosis, frequently characterized the allergic reaction. The fact that both conditions occur frequently in young adults otherwise in good health adds to the difficulty of the differential diagnosis. To us, however, it is not clearly established that the patients with an allergic condition are more likely to have such abnormal cells in the blood as a specific change resulting from their allergic states.

The importance of jaundice as a complication of infectious mononucleosis is emphasized by Spring.[236] He cites the work of de Vries,[237] who classifies the types of jaundice occurring in the course of this disease as follows: (1) jaundice as the first symptom, followed by glandular enlargement; (2) jaundice occurring along with glandular enlargement, and (3) jaundice, with or without fever, occurring as the only symptom.

236. Spring, M.: Jaundice in Infectious Mononucleosis, Bull. U. S. Army M. Dept., 1944, no. 81, p. 102.

237. deVries, S. I.: The Icteric Form of Glandular Fever. Acta med. Scandinav. 95:552, 1938.

In cases of the last type the blood picture and heterophile antibody. reaction justify the diagnosis of glandular fever. Five cases are presented and discussed in detail, illustrating each of the three types as given by deVries. Prodromal symptoms preceding the onset of jaundice are characterized by those of acute hepatitis, namely, anorexia, nausea and at times vomiting and pain or distress in the epigastric region or in the right upper quadrant of the abdomen or in both. To the fully developed clinical picture are added jaundice, enlargement of the liver, hyperbilirubinemia, urobilinuria, biluria and impaired hepatic function. Laboratory studies show an icterus index which may rise as high as 50 units, with a serum bilirubin of 8 mg. per hundred cubic centimeters. The van den Bergh reaction is reported as being direct, delayed, indirect or biphasic. *The hepatitis may last from two to twenty-two days.* In 50 to 80 per cent of the cases the heterophile antibody reaction is positive. Spring feels that the hepatitis is definitely a part of the picture of infectious mononucleosis. The etiologic agent or its toxin probably attacks some portion of the liver itself. He accepts.this view as opposed to the other explanation which · has been offered, namely. that of enlargement of the lymph nodes about the hilus of the liver causing obstructive jaundice.

. The case of a 19 year old youth who had an unusually severe case of *infectious mononucleosis simulating atypical typhoid fever is reported by* Boger.[238] The height of the temperature was 105.2 F., which is unusual for a patient with infectious mononucleosis. Likewise, the patient's *amnesia for a week is not commonly encountered in this disease.* It is of interest to note that the patient had a pertussis-like cough, which was so severe that it produced blood-streaked sputum and hoarseness, which persisted for more than two months. The report by Ziegler[216] mentioned in this review, in which he gives the findings in a fatal case of infectious mononucleosis, provides a basis for the pulmonary symptoms. Special attention in this report is devoted to the presence of jaundice in patients with infectious mononucleosis. Twenty-seven cases of jaundice are cited from the literature. It is the author's opinion that, although the jaundice has been explained on the basis of glandular obstruction, it would seem that obstruction of the biliary canaliculi due to intrinsic hepatic damage is more likely to account for this symptom. At present, however, the matter must be considered as unsettled.

The case of a 22 year old sailor is reported by Monat,[239] in which there were chills, fever, sore throat, nasal congestion and general

238. Boger, W. P.: Infectious Mononucleosis of Unusual Severity, with Review of Jaundice Cases Occurring in This Disease, South. M. J. **37**:546, 1944.

239. Monat, H. A.: Infectious Mononucleosis Simulating Acute Infectious Jaundice, Rev. Gastroenterol. **11**:114, 1944.

malaise. Four days later tenderness in the right upper quadrant of the abdomen and a moderate general adenopathy developed. There was definite jaundice of the scleras, with an icterus index which reached a maximum of about 82. The patient was febrile, with the peak temperature reaching 104 F. The typical evidences of infectious mononucleosis were present in the blood, with a sheep cell agglutination in a titer of 1:224 by Davidsohn's technic. The case is reported to point out the importance of infectious mononucleosis as a basis for icterus in a young person. The icterus "probably was due to compression of the common duct by a cluster of enlarged lymph glands," according to Monat. He thought that the absence of hepatic damage was shown by a negative result of a Hanger test, the normal duodenal drainage sequence, the fact that no organisms were grown on culture of the bile and the rapid clearing of icterus.

Two cases of infectious mononucleosis in which jaundice was present are reported by Morris, Robbins and Richter.[240] It is pointed out that in the absence of hemolysis and with an increased level of urobilinogen associated with a strongly positive cephalin flocculation reaction the presence of hepatic damage is strongly suggestive. The view is favored that when jaundice occurs in infectious mononucleosis it is not the result of pressure of enlarged glands in the liver but is dependent on actual parenchymal hepatic damage. It is also pointed out that infectious mononucleosis with hepatitis is a definite clinical picture and may occur without the presence of adenopathy and may require considerable laboratory study for its interpretation.

LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

General Observations.—Attempts to clarify the confusion of thought regarding the group of diseases classed as lymphomas continue to occupy the attention of authors. The inherent disadvantage under which all such attempts at classification labor is the necessity of basing them on morphologic changes which do not reflect differences in causation, clinical progress or response to therapy. Gonski and Holman [241] propose the following classification:

A. Lymphomas arising from lymphocytes and their precursors
   1. Lymphoblastic tumors
   2. Lymphocytic tumors
   3. Follicular tumors

240. Morris, M. H.; Robbins, A., and Richter, E.: Acute Infectious Mononucleosis with Hepatitis: Presentation of Two Cases, New York State J. Med. **44**:1579, 1944.

241. Gonski, A., and Holman, S.: The Lymphomata: A Suggested New Classification and General Clinical Features, Leech **14**:17, 1944.

B. Lymphomas arising from reticular cells
 1. Diffuse
   a. Hodgkin's disease
   b. Monocytic leukemia
   c. Aleukemic reticuloendotheliosis
   d. Letterer-Siwe's disease
   e. Boeck's sarcoid (probably)
 2. Localized
   a. Malignant monoblastoma
   b. One variety of reticulum cell sarcoma
C. Lymphomas arising from littoral cells (local histiocytes)
 1. Diffuse
   a. Clasmatocytic leukemia
   b. Stengel-Wolbach sclerosis, or diffuse littoral cell overgrowth
 2. Localized (a variety of littoral cell [histiocyte] sarcomas, or large-celled lymphosarcomas)

The surgical excision of malignant lymphomas is discussed by Gall,[242] who reports a series of 48 cases representing all types of such tumors in which there was sufficient localization to permit radical surgical removal of the affected lymph tissue.. The average duration of life after operation was 5.2 years, and the average total duration after the onset of symptoms was 6.9 years. The prognosis for the surgically treated patients compared favorably with that for patients whose treatment was limited to irradiation. Twenty of the patients were without residual evidences of lymphoma. The author believes that radical surgical intervention has a definite place in the treatment of certain patients with malignant lymphoma.

Hodgkin's Disease.—Three histologically and clinically distinct types of Hodgkin's disease are recognized by Jackson and Parker.[243] The presence of Sternberg-Reed cells is necessary for diagnosis in all types. Hodgkin's paragranuloma, the most benign form of the disease, is characterized by relatively few Sternberg-Reed cells with many lymphocytes and without necrosis or fibrosis or evidence of invasion of the capsule of the gland. This form is essentially a disease of lymph nodes. It is compatible with a practically normal life for many years and has all the indications of being an infectious process. It may or may not become transformed into the more malignant type, Hodgkin's granuloma.

242. Gall, E. A.: The Surgical Treatment of Malignant Lymphoma, Ann. Surg. **118**:1064, 1943.

243. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease: General Considerations, New England J. Med. **230**:1, 1944; Hodgkin's Disease: Pathology, ibid. **231**:35, 1944. Jackson, H., Jr.: Hodgkin's Disease, Bull. New England M. Center **6**:216, 1944.

The histologic pattern of the granulomatous forms includes many Sternberg-Reed cells, which the authors believe arise from the reticulum, conspicuous pleomorphism, infiltration of eosinophils, necrosis and fibrosis. Hodgkin's granuloma may involve any organ or tissue, except the central nervous system proper. The spleen, liver and gastro-intestinal tract are frequently affected. It is the classic type of the disease and is considered by some as a neoplasm and by others as an infection. Jackson and Parker consider that the histopathologic features, clinical course and type of fever are all indicative of the infectious nature of the process. The third and most malignant form of the disease, Hodgkin's sarcoma, has all the features of a true neoplasm with highly invasive properties. It tends to occur in an older age group than do the two less malignant forms of the disease, and it may involve any organs, including the central nervous system. Hodgkin's sarcoma is distinguished from reticulum cell sarcoma by the presence of Sternberg-Reed cells. The predominant cells are probably extremely anaplastic, relatively small forms of Sternberg-Reed cells, with frequent mitoses. Transition forms of the three types of Hodgkin's disease may occur, and a more benign type may and frequently does progress to a more malignant one, but regression to a state of lessened malignancy never takes place. The authors discuss theories of etiology of Hodgkin's disease and consider that neither tuberculosis nor brucellosis have any etiologic relation to the condition. Their data indicate that Hodgkin's disease is the cause of 0.25 per cent of deaths in a general hospital.

In the University Medical Clinic, Basel, Switzerland, 126 cases of lymphogranuloma were observed in the years 1920 to 1942 inclusive, according to Lüdin.[244] Among these, 65 of the patients were females and 61 were males. The total number of patients seen during these years was 55,738, giving an incidence of lymphogranuloma of 0.226 per cent. The greatest number of patients with lymphogranuloma, 45 per cent of the total, were in the third decade of life, and this age preponderance applied both to men and to women. There were two instances of familial occurrence of the disease, in one a brother and sister and in another a mother and daughter were affected. In 3 cases the lymphogranuloma was complicated by pregnancy, and in 2 the pregnancy appeared to cause aggravation of the process. The 3 children resulting from these pregnancies were healthy when observed at the ages of 15, 8 and 4 years, respectively. One of the mothers died of lymphogranuloma nine years after her pregnancy; 1 died three

244. Lüdin, M.: Ueber Lymphogranulomatose; Diagnose und Therapie, Strählentherapie **74**:367, 1944.

years later, and the third was living four years after delivery. The author emphasizes that all patients with enlargement of the peripheral lymph nodes should have a roentgen examination of the chest, even though biopsy of a lymph node fails to establish a diagnosis. He cites such an instance in which enlargement of the mediastinal lymph nodes was found and the condition was later proved to be lymphogranuloma. In 2 of the patients reported on primary localization of the disease appeared to be in the tonsil. Lüdin discusses the symptoms, physical signs and blood values in lymphogranuloma. Leukocyte counts greater than 10,000 per cubic millimeter were observed in 67 per cent of the patients, the increase being due to neutrophils. There was a shift to more immature neutrophils in 38.2 per cent. Eosinophilia, amounting to more than 5 per cent of the circulating leukocytes, was found in only 3.4 per cent. Lymphocytopenia occurred in 94.3 per cent, monocytosis in 26.1 per cent, hypochromic anemia in 27.2 per cent and acceleration of the sedimentation rate in 97.8 per cent. For the clinical diagnosis of lymphogranuloma the author considers that the most important criteria are enlargement of the lymph nodes, intermittent fever, neutrophilic leukocytosis, lymphocytopenia and rapid sedimentation rate. Cases with involvement of bone are described, and irradiation therapy of the disease is discussed.

The case histories of 244 patients for whom the diagnosis of Hodgkin's disease was made at the Edward Hines Hospital, Washington, D. C., from 1930 to 1940 inclusive, were reviewed by Bersack.[245] Of these, 19 were excluded because of lack of biopsy, inadequate data or erroneous diagnosis. The patients in the remaining 225 cases were studied with particular reference to the determination of prognosis on the basis of the nature of the histologic changes. Necropsies were performed on 67 of the patients. The author concludes that favorable elements in the histologic picture of Hodgkin's disease comprise preservation of the follicles, absence of capsular invasion, fibrosis, trabeculation or tendency to giant follicle formation, vascularity, presence of fibroblast-like cells and persistence in abundance of the small lymphocytic elements of the node. The extent of tissue involvement bore a direct relation to the rapidity of the course of the disease. Involvement of the inguinal nodes appeared to have the same prognostic significance as generalized dissemination of the process. The lymphoreticuloma type with sarcomatous features was the most frequently occurring form of Hodgkin's disease after the age of 40 years and carried a relatively poor prognosis.

245. Bersack, S. R.: Hodgkin's Disease—Incidence and Prognosis: Statistical Correlation with Clinicopathologic Picture, Arch. Int. Med. **73**:232 (March) 1944.

Among 3,450 hospital patients there were 18 with Hodgkin's disease and 18 with pseudoleukemia (lymphadenoma?), according to Floros.[246] A history of tuberculosis was obtained from 2 of the patients with Hodgkin's disease. Irradiation was the most effective form of therapy employed. Other measures included arsenical, iron and liver preparations. Fifty-two cases of Hodgkin's disease are reviewed by Oakey.[247] There were no demonstrable predisposing or etiologic factors. Males comprised 69.2 per cent of the patients. The highest percentage of cases occurred in the age range of 50 to 60 years. The cervical region was involved primarily in 59.6 per cent, with unilateral involvement more common than bilateral. The average duration of life of 33 of the patients, presumably from the time of their initial observation, was 20.3 months. Two patients were alive five years after the first examination.

Involvement of the bone marrow in Hodgkin's disease is discussed by Steiner,[248] who reviews the literature on the subject and reports an analysis of 14 cases, in 11 of which microscopic examination of small samples of marrow revealed the changes of Hodgkin's disease. The bones were selected at random, and in thirty-eight of sixty-two sections studied evidence of Hodgkin's disease was found. The author believes that in practically every case of Hodgkin's disease lesions of the marrow would be found if enough bones could be thoroughly examined. The pain occurring in Hodgkin's disease, he thinks, may be attributed to osseous involvement. Because of the sparsity of lesions, however, it is not usually possible to explain the anemia on the basis of replacement of marrow. Aspiration of sternal marrow ordinarily fails to reveal evidence of Hodgkin's disease. Steiner points out that the distribution of the lesions in Hodgkin's disease follows more closely that of the reticuloendothelial system than that of the lymphatic system.

Vascular involvement by the lesions of Hodgkin's disease is reviewed by Salvador Júnior.[249] His own observations are based on the study of 19 cases. The changes in the vessels in Hodgkin's disease include: (1) early and extensive mobilization of endothelial elements in both blood and lymph capillaries, (2) infiltration of the walls of the capillaries by leukocytes and red blood cells, (3) in the larger vessels,

246. Floros, A.: Beobachtungen bei 18 Fällen vòn Lymphogranulomatose, Wien. klin. Wchnschr. **56**:270, 1943.

247. Oakey, R. S., Jr.: Review of Fifty-Two Cases of Hodgkin's Disease, Hahneman. Monthly **79**:139, 1944.

248. Steiner, P. E.: Hodgkin's Disease: The Incidence, Distribution, Nature and Possible Significance of the Lymphogranulomatous Lesions· in the Bone Marrow: A Review with Original Data, Arch. Path. **36**:627 (Dec.) 1943.

249. Salvador Júnior, A.: As lesões vasculares no granuloma maligno, Portugal méd., 1943, no. 4, p. 151.

more often arteries than veins, a proliferative and obliterative "endovascularitis," frequently associated with thrombosis, (4) a "perivascularitis" also affecting the larger vessels and (5) in later stages invasion of the vessel wall by granulomatous tissue, occasionally resulting in thrombophlebitis or hemorrhage. In 4 cases diffuse necrosis secondary to vascular involvement was observed. In all cases sclerosis of vessels of varying degree was found. The author concludes that the vascular modifications occurring in Hodgkin's disease are a characteristic feature of the disease.

Intrathoracic involvement was proved by roentgen examination in 63 per cent of 55 cases of Hodgkin's disease reported by Wolpaw, Higley and Hauser.[250] However, their patients probably represent a selected group.

Actuated by earlier published reports by Parsons and Poston of the coexistence of Hodgkin's disease and brucellosis, Hoster, Doan and Schomacher [251] attempted without success to isolate organisms of the Brucella group from the tissues and body fluids of 35 patients with Hodgkin's disease and of 36 patients with miscellaneous diseases of the reticuloendothelial system.

The case of a woman aged 52 is reported by Anderson.[252] Necropsy revealed generalized enlargement of lymph nodes and splenomegaly. There was proliferation in the sinuses and medullas of histiocytic elements and of atypical cells classified as prohistiocytes. These were large cells of polygonal shape possessing nuclei rich in chromatin and with prominent nucleoli. The author points out that this condition had been previously separated from the group of diseases commonly classed as atypical Hodgkin's disease. Grossman [253] reports the case of a 68 year old woman with Hodgkin's disease, apparently limited to the abdominal cavity and complicated by macrocytic anemia and a megaloblastic reaction of the marrow which was refractory to liver therapy. The clinical course was rapidly progressive and was marked by high fever. Necropsy revealed atrophy of the gastric mucosa and patches of Hodgkin's granuloma with many megaloblasts in the bone marrow. The question whether the patient had pernicious anemia as well as

250. Wolpaw, S. E.; Higley, C. S., and Hauser, H.: Intrathoracic Hodgkin's Disease, Am. J. Roentgenol. 52:374, 1944.

251. Hoster, H. A.; Doan, C. A., and Schomacher, M.: Studies in Hodgkin's Syndrome: A Search for Brucella in Hodgkin's Syndrome, Proc. Soc. Exper. Biol. & Med. 57:86, 1944.

252. Anderson, R. G.: Histiocytic Medullary Reticulosis with Transient Skin Lesions, Brit. M. J. 1:220, 1944.

253. Grossman, E. B.: Abdominal Hodgkin's Disease: No Superficial Lymph Node Enlargement; Macrocytic Anemia Resistant to Liver Therapy, J. Mt. Sinai Hosp. 10:804, 1944.

Hodgkin's disease was left undecided. An unusual leukocyte picture presented by a woman of 78 with Hodgkin's disease is reported by Williams and Neubuerger.[254] The duration of the illness was about six months. Lymphadenopathy, hepatomegaly and splenomegaly were present, and the patient failed to benefit from roentgen ray therapy. The erythrocyte count was 2,240,000 per cubic millimeter, hemoglobin value 8.5 Gm. per hundred cubic centimeters and leukocyte count 140,000 per cubic millimeter, with a differential count of eosinophils 52.3 per cent, neutrophils 44.2 per cent, including a few myelocytes, and lymphocytes 3.3 per cent. The diagnosis was confirmed by necropsy.

A man aged 38 suffering with Hodgkin's disease, thrombopenic purpura and pulmonary tuberculosis was observed by Wright-Smith.[255] At necropsy generalized Hodgkin's disease involving the bone marrow was found. Tuberculosis was limited to the lungs. Simon[256] reports the case of a 56 year old man with Hodgkin's disease terminating in acute miliary tuberculosis. Ayerza and Cernich[257] observed a man of 38 with Hodgkin's disease complicated by pericarditis.

The case of a man aged 39 with Hodgkin's disease and disturbed vitamin A metabolism is reported by Glazebrook and Tomaszewski.[258] There was evidence of severe impairment of hepatic function and increased excretion of vitamin A, especially during febrile episodes. The patient had a generalized ichthyosiform atrophy of the skin, which was thought possibly to be the result of the abnormal metabolism of vitamin A. Sabetta[259] reports the case of a woman of 64 without enlargement of the liver, spleen or lymph nodes, with the exception of one epitrochlear node, which was removed and found to reveal Hodgkin's disease. There was a scattered erythematous papular eruption on the arms, shoulders, chest, hips and thighs. Levin[260] observed a Negro aged 32 with pea-sized to quarter-sized tender nodules of the skin of

254. Williams, W. S., and Neubuerger, K. T.: ·Hodgkin's Disease with Marked Eosinophilia, Rocky Mountain M. J. **41**:320, 1944.

255. Wright-Smith, R. J.: A Case of Hodgkin's Disease with Thrombocytopenic Purpura Complicating Chronic Pulmonary Tuberculosis, Roy. Melbourne Hosp. Clin. Rep. **14**:70, 1943.

256. Simon, S. M.: Hodgkin's Disease with Terminal Miliary Tuberculosis, M. Bull. Vet. Admin. **21**:97, 1945.

257. Ayerza, L., and Cernich, R.: Granuloma maligno primitivo del pericardio (caso princeps), Rev. Asoc. méd. argent. **57**:981, 1943.

258. Glazebrook, A. J., and Tomaszewski, W.: Ichthyosiform Atrophy of the Skin in Hodgkin's Disease: Report of a Case, with Reference to Vitamin A Metabolism, Arch. Dermat. & Syph. **50**:85 (Aug.) 1944.

259. Sabetta, A.: Hodgkin's Disease of the Skin, Arch. Dermat. & Syph. **49**:289 (April) 1944.

260. Levin, O. L.: Hodgkin's Disease of the Skin in a Negro, Arch. Dermat. & Syph. **49**:75 (Jan.) 1944.

the upper anterior surface of the thorax. Biopsy of one of these nodules as well as of a supraclavicular lymph node revealed the presence of Hodgkin's disease.

Mycosis fungoides apparently bears a relation to Hodgkin's disease which is not well understood. Grandbois [261] reports the case of a man of 69 with generalized cutaneous involvement and erythroderma considered to be due to mycosis fungoides. The leukocyte count reached the level of 48,000 per cubic millimeter, and 60 per cent of the cells were classified as atypical monocytes.

Uveitis believed to be directly associated with Hodgkin's disease is reported in a man of 26 by Kamellin. [262] Canfield [263] reports the case of a man aged 28 who twelve years earlier had a diagnosis made of Hodgkin's disease on the basis of biopsy of an enlarged axillary node. At that time he received roentgen ray therapy, and he was able shortly before coming under the author's observation to pass an army induction examination. Soon after he entered the armed forces, a proliferating granulomatous mass developed on the vocal cords. A diagnosis of Hodgkin's disease was made on the basis of examination of the tissue. The lesion rapidly progressed.

The case of a man of 60 with Hodgkin's disease of the stomach is reported by Jungmann. [264] Total gastrectomy and splenectomy were performed in the belief that the patient had a carcinoma of the stomach. The author suggests that the discrepancy between the extent of the changes in the mucous membrane and the persistence of peristalsis, as revealed by roentgen examination and gastroscopy, may be of value in differentiating carcinoma from lymphogranuloma of the stomach. Atypical Hodgkin's disease in a woman of 44 years, apparently limited to a small portion of ileum, is reported by Donati and Bragaglia. [265] Four months after resection of the affected portion of the intestine the patient was apparently well. The coexistence of metastatic epithelioma and malignant granuloma in a woman aged 67 is reported by Sammartino. [266]

261. Grandbois, J.: Mycosis fongoïde à forme érythrodermique et à formules sanguines pseudo-leucémiques, Laval méd. **8:**695, 1943.

262. Kamellin, S.: Uveitis Associated with Hodgkin's Disease: Report of Case, Arch. Ophth. **31:**517 (June) 1944.

263. Canfield, N.: Laryngeal Obstruction Probably Due to Hodgkin's Disease, Proc. Roy. Soc. Med. **37:**673, 1944.

264. Jungmann, H.: Hodgkin's Disease of Stomach, Brit. J. Radiol. **16:**386, 1943.

265. Donati, A., and Bragaglia, R.: Linfogranuloma maligno primitivo de intestino com especiais caracteres blastomatosos de glandulas mesenteriais (contribuição ao estudo das formas atipicas de morbo de Hodgkin), Folia clin. et biol. **14:**103, 1942.

Surgical excisions of affected lymph nodes in 2 cases of Hodgkin's disease is reported by Puente Duany.[267] In both patients the disease later became generalized.

Lymphosarcoma.—During a nine year period 20 cases of lymphosarcoma of the gastrointestinal tract were observed at the New York Hospital, according to McSwain and Beal.[268] The total number of admissions in this period was 149,469. The ratio of lymphosarcoma to carcinoma is 1 : 51, or 1.9 per cent of all malignant lesions of the gastrointestinal tract. In their series, involvement of all parts of the tract except the duodenum was represented. It is advised that such tumors should be extirpated when possible and that irradiation therapy should always be employed. Rafsky, Katz and Krieger[269] report 11 cases of proved lymphosarcoma of the stomach and 1 in which this diagnosis was probable. All the patients were operated on. Their ages ranged from 18 to 80 years, and the clinical manifestations were variable. A case of lymphosarcoma of the stomach in which the tumor was not revealed by roentgen examination but was seen by means of the gastroscope is reported by Paul and Parkin.[270]

According to Winkelstein and Levy,[271] lymphosarcoma of the intestine is rare, more often affecting the small than the large bowel. Multiple lesions are not uncommon. The neoplasm may develop at any age, the average in their series being 43.7 years. The most common clinical manifestations are abdominal pain, loss of weight, pallor and the presence of an abdominal mass. The condition is always fatal, and even when both surgical and roentgen therapy are employed the duration of life after initial treatment is usually less than one year. Mena[272] reports the case of a man of 40 years who had suffered with episodes of abdominal pain and bloody diarrhea for two years, in whom acute intestinal obstruction finally developed. Necropsy revealed lymphosarcoma, with ulcerations involving portions of the ileum and jejunum. The patient also had a hydatid cyst of the liver.

266. Sammartino, R.: Epitelioma y granuloma maligno concomitantes, Arch. Soc. argent. de anat., norm. y pat. **4**:48, 1942.

267. Puente Duany, N.: Dos casos de enfermedad de Hodgkin a punto de partida localizado y en sitios poco frecuentes; posibilidades quirúrgicas de la enfermedad, Arch. cubanos cancerol. **2**:189, 1943.

268. McSwain, B., and Beal, J. M.: Lymphosarcoma of the Gastrointestinal Tract: Report of Twenty Cases, Ann. Surg. **119**:108, 1944.

269. Rafsky, H. A.; Katz, H., and Krieger, C. I.: Varied Clinical Manifestations of Lymphosarcoma of the Stomach, Gastroenterology **3**:297, 1944.

270. Paul, W. D., and Parkin, G. L.: Lymphosarcoma of the Stomach: A Gastroscopic Report, Gastroenterology **3**:214, 1944.

271. Winkelstein, A., and Levy, M. H.: Lymphosarcoma of Intestines: Fifteen Cases; Characteristic Sigmoidoscopic Picture, Gastroenterology **1**:1093, 1943.

272. Mena R., I.: Linfosarcoma del intestino, Rev. méd. de Chile **71**:800, 1943.

The case of a man aged 39 with lymphosarcoma of the cecum is reported by Harper, Waugh and Dockerty.[273] The tumor was successfully resected, and subsequently irradiation therapy was given. The authors point out that the behavior of lymphosarcoma of the intestine varies greatly with respect to symptoms, response to treatment and duration of life. They state that the occurrence of intussusception in an adult should always suggest the possibility of lymphosarcoma of the cecum.

Lymphosarcoma of the urinary bladder is very rare, according to Rathbun and Wehrbein,[274] who report a case and were able to find but 5 others described in the literature. Their patient was a 64 year old man with a history of recurrent cystitis extending over a period of ten years. Several tumors were present in the bladder wall, covered by intact mucosa. The rarity of the condition is attributed to the absence normally of lymph tissue in the bladder. As the result of prolonged infection deposition of lymph tissue, which may become sarcomatous, occurs.

Osseous involvement by lymphosarcoma is discussed by Bianchi and Muscolo,[275] who report the case of a boy of 17 years with roentgenologic and histologic evidence of invasion of the bones of the pelvic girdle. The primary lesions apparently occurred in a submaxillary node. Later the skull and one tibia and fibula became involved.

A girl aged 13 who exhibited generalized invasion of blood vessels by tumor cells of small lymphocytes is reported on by Radzinski and Uznanski.[276] There was no evidence of escape of neoplastic cells into the blood stream. Early and extensive involvement of the central nervous system occurred, associated with meningeal and cerebral symptoms.

Giant follicular lymphoblastoma involving the spleen and axillary and inguinal lymph nodes occurring in a man of 32 is reported on by Murray and Storr.[277] The patient was apparently well four years after roentgen therapy. Evans [278] points out that the histologic pattern of lymphadenitis of secondary syphilis closely resembles that of giant

273. Harper, S. B.; Waugh, J. M., and Dockerty, A. B.: Lymphosarcoma of Cecum: Report of Case, Proc. Staff Meet., Mayo Clin. **19**:182, 1944.

274. Rathbun, N. P., and Wehrbein, H. L.: Lymphosarcoma of the Urinary Bladder, J. Urol. **51**:31, 1944.

275. Bianchi, 'A., and Muscolo, D.: Linfosarcomatosis con lesiones óseas, Rev. ortop. y traumatol. **13**:79, 1943.

276. Radzinski, J. M., and Uznanski, M. E.: Generalized Lymphosarcomatosis with Marked Involvement of Brain, Illinois M. J. **85**:87, 1944.

277. Murray, J. F., and Storr, N. V.: Giant Follicular Lymphoblastoma: Report of a Case, Clin. Proc. **3**:244, 1944.

278. Evans, N.: Lymphadenitis of Secondary Syphilis: Its Resemblance to Giant Follicular Lymphadenopathy, Arch. Path. **37**:175 (March) 1944.

follicular lymphadenopathy. He cites 2 cases, in both of which Treponema pallidum was demonstrated in the affected nodes.

Puente Duany[279] studied the cellular elements of lymph tissue in healthy persons and in patients with various, pathologic conditions. He found that more satisfactory morphologic examination could be performed with imprint preparations than with histologic sections. As material for general study of lymph tissue the tonsils are recommended.

Leukemia.—An analysis of 357 cases of leukemia observed at the Cleveland Clinic over a thirteen year period is presented by Haden.[280] Of these, 50 were classified as monocytic leukemia, 60 as acute myeloid, 90 as chronic myeloid, 54 as acute lymphoid and 101 as chronic lymphoid leukemia. The author emphasizes that toxemia and infiltration of organs are responsible for most of the clinical manifestations of leukemia. The youngest patient ·in the series was 3½ years old and suffered with monocytic leukemia; the oldest, 76 years of age, had chronic myelogenous leukemia. Monocytic and acute myelogenous leukemia affected all age groups about equally. Acute lymphogenous leukemia was most common in children; chronic lymphogenous leukemia occurred most frequently in persons of middle age. In one third of the cases, the leukocyte count did not exceed 10,000 per cubic millimeter. Patients with monocytic leukemia often suffered with hyperplasia of the gums and infections of the oral cavity. Acute lymphogenous leukemia was commonly accompanied with anemia, bleeding and arthritis. Acute myelogenous leukemia was characterized by a great variety of symptoms and signs. Chronic lymphogenous leukemia often pursued a relatively benign course. In patients with chronic myelogenous leukemia, toxemia, fever and anemia were conspicuous features.

A classification of neoplastic diseases affecting lymphatic, myeloid and reticuloendothelial tissues is given by Hadorn.[281] The cells of the reticuloendothelium are subdivided into those of reticulum and plasma cell types. Neoplastic disease of these tissues may be localized, generalized or leukemic.

An important monograph by Stodtmeister and Büchmann[282] deals with the pathology and disturbances of myeloid function in aplastic

279. Puente Duany, N.: Estudio comparativo de las celulas normales y patológicas del sistema linfoideo y en particular aquellas de los tumores y lesiones malignas de los ganglios linfáticos, Bol. Liga contra el cáncer **19**:45, 1944.

280. Haden, R. L.: Varying Clinical Picture of Leukemia (Edwin R. Kretschmer Memorial Lecture), Proc. Inst. Med. Chicago **15**:98, 1944. Haden, R. L.: The Leukemias, Cleveland Clin. Quart. **11**:55, 1944.

281. Hadorn, W.: Ueber Leukaemie und Leukosen, Praxis **33**:375, 1944.

282. Stodtmeister, R., and Büchmann, P.: Die funktionell-pathologischen Beziehungen zwischen aplastischer Anämie und akuten Leukämien, Ergebn. d. inn. Med. u. Kinderh. **60**:367, 1941.

anemia and acute leukemia. With reference to the pathogenesis of acute leukemia, the authors conclude that despite the extraordinary pleomorphism of the disease it is essentially a single or unified pathologic process. The apparent hyperplasia of marrow seen often in cases of aplastic anemia is explained by the authors as an inadequate or incomplete reactive process representing an effort at compensation for the panmyelophthisis. Evenually this disordered myeloid hyperplasia may lead to extramedullary hemopoiesis. The ultimate result may be either panmyelophthisis with fat replacement or malignant degeneration, constituting leukemia. This article, itself a review, with about 250 references to the literature, is too comprehensive for adequate treatment here and should be studied by all who are interested in the subject.

The neurologic complications of leukemia are discussed by Stodtmeister and Weicker,[283] who collected the data afforded by 300 cases presenting such complications reported in the literature. They conclude that involvement of the nervous system is not an unusual complication of leukemia and may be due to hemorrhage, infiltration or degeneration. Hemorrhagic manifestations are most common in the myeloblastic phase of chronic myelogenous leukemia and in acute myelogenous leukemia. Nervous manifestations due to pressure may result from the development of chloroma tumors in myeloblastic leukemia. Leukemic infiltration occurs especially often in chronic lymphatic leukemia, which is also frequently associated with herpes zoster. Degenerative changes in the nervous system occurring in leukemia are of obscure origin and cannot be correlated with any special form of the disease.

A series of cases, comprising 53 of chronic myelogenous leukemia and 13 of chronic lymphogenous leukemia, were studied by Grinschpun and Raventós.[284] In the myelogenous group, 38 of the patients were males and 15 were females. The average age of the males was 36.4 years and that of the females 32.8 years, whereas the extreme ages were 6 and 54 years. In this series there were two brothers with leukemia. Priapism was noted as a complication in 6 of the patients—a much higher incidence than that usually observed. Pruritus occurred frequently in patients with chronic lymphogenous leukemia. In a second article, dealing with treatment, the same authors [285] report their

283. Stodtmeister, R., and Weicker, H.: Leukämie und Krankheiten des Nervensystems, Med. Klin. **39**:551, 1943.

284. Grinschpun, S., and Raventós, E.: Estudios sobre leucemias crónicas: Casuística, sintomatología, complicaciones, hematología, y anatomía patologíca, Rev. méd. de Chile **71**:878, 1943.

285. Grinschpun, S., and Raventós, E.: Estudios sobre leucemias crónicas: Tratamiento de las leucemias, Rev. méd. de Chile **71**:1068, 1943.

results with local roentgen irradiation over the spleen, roentgen irradiation of the whole body and radium irradiation of the spleen in cases of chronic myelogenous leukemia. The results obtained from these several forms of therapy were approximately the same with respect to initial response to treatment and duration of remission. The authors observed that the response to irradiation therapy in cases of lymphogenous leukemia was slower than in cases of the myelogenous variety and that the duration of remissions in the former type was shorter. They advocate the use of arsenic in the form of solution of potassium arsenite (Fowler's solution) between courses of irradiation therapy in the treatment of leukemia.

The roentgen therapy of leukemia is discussed by Athle,[286] who reports temporary improvement after such treatment in 12 cases of chronic myelogenous leukemia and 1 of chronic lymphogenous leukemia. No benefit following roentgen irradiation was observed in 1 case of myelogenous leukemia and 1 of lymphosarcoma with leukemia.

Uhlmann and Goldner [287] believe that the elevated basal metabolic rate in leukemia is an expression of the high oxygen requirement of leukemic cells. This behavior is unlike that of other neoplastic diseases, in which malignant cells demonstrate a high degree of aerobic glycolysis and a relatively small degree of oxygen consumption. The authors present case records in support of their contention that the basal metabolic rate is preferable to the blood count as a laboratory guide in the roentgen treatment of leukemia. They found that as a rule the metabolic rate was elevated when an exacerbation of the disease was approaching and that the rate was decreased as soon as therapy became effective, a change that could be observed usually long before other clinical or laboratory manifestations became apparent. It was felt that by employing the basal metabolic rate as a guide it was possible to control the leukemic process by the use of relatively small amounts of roentgen radiation.

The present status of radioactive phosphorus in the treatment of the leukemias is reviewed by Webster.[288] In this excellent essay by a medical student, the published reports of the use of labeled phosphorus (P_{32}) are summarized and the conclusion is reached that this form of therapy is of value in the management of patients with chronic forms of leukemia but that it is useless or deleterious in the treatment of those with acute leukemia.

286. Athle, L. H.: Radiation Therapy of Leukemia, M. Bull., Bombay **11**: 461, 1943.

287. Uhlmann, E. M., and Goldner, M.: Use of Basal Metabolic Rate in Management of Radiotherapy for Leukemia, Radiology **42**:165, 1944.

288. Webster, C.: The Use of Radio-Active Phosphorus in the Treatment of Leukemia, Texas Rep. Biol. & Med. **2**:83, 1944.

The radioactive isotope of phosphorus P_{32} is commonly prepared by the bombardment in the cyclotron of iron phosphide, a highly insoluble compound. From this substance it is the usual practice to prepare dibasic sodium phosphate (Na_2HPO), a procedure which is attended with some difficulty. Warren and Cowing [289] state that phosphoric acid (H_3PO_4) and magnesium ammonium phosphate ($MgNH_4PO_4$) are both more readily prepared from iron phosphide than is the dibasic sodium salt and that these compounds may be safely administered by the intravenous route when dissolved in 250 to 300 cc. of a solution containing 0.85 Gm. of sodium chloride and 5 Gm. of dextrose per hundred cubic centimeters for each therapeutic dose. The retention of labeled phosphorus was practically identical after administration of the three compounds tested.

That radioactive phosphorus exerts a potent and potentially deleterious influence on the elements of normal blood formation is demonstrated by the observations of Hempelmann and his associates,[290] who noted leukopenia, thrombopenia or anemia attributable to the medication in approximately one third of their patients who had received this material. The changes in the myeloid elements were not necessarily parallel. The conditions for which treatment with P_{32} was employed included chronic myelogenous leukemia, chronic lymphogenous leukemia and monocytic leukemia, leukosarcoma, Hodgkin's disease, reticulum cell sarcoma, polycythemia vera, multiple myeloma and mycosis fungoides. The authors state that the reduction of leukocytes or platelets may be so severe as to produce clinical manifestations and that the development of thrombopenia in patients treated for leukemia may be delayed for one or two months after the leukocyte count has decreased to approximately normal levels. The advisability of frequent blood studies during and after treatment with radioactive phosphorus is emphasized.

The results of roentgen therapy in a series of cases representing miscellaneous conditions are reported by Lessard.[291] Nine patients with chronic myelogenous leukemia, 2 with chronic lymphogenous leukemia, 1 with acute myelogenous leukemia, 11 with Hodgkin's disease and 14 with lymphosarcoma were treated. The patient with acute myelogenous leukemia died two months after the onset of symptoms and failed to benefit, even temporarily, from roentgen ray therapy.

289. Warren, S., and Cowing, R. F.: The Retention of Radioactive Phosphorus When Administered in Different Chemical Forms, Cancer Research **4**:113, 1944.

290. Hempelmann, L. A., Jr., and others: Hematologic Complications of Therapy with Radioactive Phosphorus, J. A. M. A. **124**:735 (March 11) 1944.

291. Lessard, R.: Quelques résultats obtenus par la radiothérapie dans les leucémies, dans les lymphosarcomes et dans la maladie de Hodgkin, Laval méd. **9**:103, 1944.

The average duration of life for 5 patients with chronic leukemia followed until their deaths, was 16.8 months. Three patients with Hodgkin's disease lived for an average of 27.6 months. The mean duration of life for 4 patients with lymphosarcoma was 8.3 months.

The role of sepsis as a complication of acute leukemia and agranulocytosis is discussed by Scharff,[292] who reports beneficial results from the use of sulfonamide preparations in the treatment of ulcerous lesions of the oral mucous membrane and other manifestations of sepsis occurring in patients with these blood disorders. In our opinion it is worthy of emphasis that the continued administration of one of the sulfanilamide derivatives, preferably sulfadiazine, is an effective means of preventing as well as treating the necrotizing infections which add so greatly to the distress of patients suffering with acute leukemia.

Two cases of leukemia associated with other forms of malignant invasion are reported by Morrison and his associates.[293] One patient, a man aged 62 years, was found to have adenocarcinoma of the rectum, and the blood at that time was reported as normal. Fifteen months later subleukemic myeloblastic leukemia developed. The second patient, a·man of 58 years, suffered from carcinoma of the head of the pancreas and chronic lymphogenous leukemia. The authors state that only 21 cases of leukemia and associated malignant growths have been reported previously in the literature. Of these, 14 were cases of lymphogenous leukemia, 6 of myelogenous leukemia and 1 of monocytic leukemia. There was no predilection for any special site or type of neoplasm. It is our view that these figures give no true picture of the actual incidence of leukemia and associated malignant growth. Lymphogenous leukemia in elderly persons is usually relatively benign and of long duration. The development of carcinoma in such patients has been, in our experience, by no means infrequent, but the association has never appeared to be more than coincidental. Gruner[294] reports the association of chronic myelogenous leukemia and carcinoma of the vulva in a woman of 26 years.

Churg and Wachstein[295] reviewed the histologic observations in 97 cases of leukemia and found evidence of varying degrees of myelofibrosis without osteosclerosis in 6. Of the 6 patients 4 had chronic myelogenous leukemia and received roentgen therapy. The remain-

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292. Scharff, O.: Zur Therapie der akuten Leukämien und der Agranulozytose, Wien. klin. Wchnschr. **57**:169, 1944.

293. Morrison, M.; Feldman, F., and Samwick, A. A.: Carcinoma and Leukemia: Report of Two Cases, with Combined Lesions; Review of Literature, Ann. Int. Med. **20**:75, 1944.

294. Gruner, W.: Leukämische Myelose unter dem Erscheinungsbild eines Vulvakarcinoms, Zentralbl. f. Gynäk. **67**:1562, 1943.

295. Churg, J., and Wachstein, M.: Osteosclerosis, Myelofibrosis and Leukemia. Am. J. M. Sc. **207**: 141, 1944.

ing 2 had subacute myelogenous leukemia and were not treated by roentgen irradiation. A case is described of osteosclerosis with a leukemoid blood picture in a woman of 60 years. The disease, diagnosed eight years before as chronic myelogenous leukemia, was interpreted as an instance of nonleukemic myelosis because of the long clinical course, the moderate elevation of the leukocyte count, with a small number of primitive cells, the constant presence of nucleated erythrocytes, chronic splenomegaly, absence of typical leukemic infiltrations and diversity of the cells in sites of myeloid metaplasia, with large numbers of megakaryocytes. The authors conclude from their observations and from a review of the literature that myelofibrosis not associated with osteosclerosis is apparently not uncommon in the leukemias and that osteosclerosis is often associated with nonleukemic myelosis but rarely if ever with true leukemia.

Two patients with leukemia in whom the disease was believed to be congenital are reported on by Cross.[296] The first, a boy born of Italian parents, was first seen at the age of 3 months. The second, a girl whose parents were Irish, was seen at the age of 1½ months. In both infants hemorrhagic manifestations had been present from birth, and for both the diagnosis of myelogenous leukemia was made at necropsy. The author states that the literature of the past twenty-five years includes reports of 20 cases of congenital leukemia, of which 16 were of myelogenous leukemia, 3 were of lymphogenous leukemia and 1 was of uncertain type.

A man 46 years old was found to have acute monocytic leukemia, and two years later acute myeloblastic leukemia developed in his sister, aged 43, who had lived in the same house, according to Meikle.[297]

Two cases of chronic lymphogenous leukemia are reported by Richardson.[298] They were considered of special interest because in one, that of a man of 68 years, the leukocyte count exceeded that of the erythrocytes, reaching a level of 1,475,000 per cubic millimeter, and in the other, that of a woman aged 67, the leukemia was without symptoms but was complicated by pneumonia. The infection responded favorably to treatment with sulfadiazine, but no effect on the leukocyte picture was observed.

An unusual case of chronic lymphogenous leukemia occurring in a woman of 58 years is described by Petit and his associates.[299] There

296. Cross, F. S.: Congenital Leucemia: Report of Two Cases, J. Pediat. **24**:191, 1944.

297. Meikle, R. W.: Two Varieties of Leukaemia in One Family, Brit. M. J. **2**:468, 1944.

298. Richardson, C. R.: Chronic Lymphatic Leukemia: Report of Two Cases, New York State J. Med. **44**:292, 1944.

299. Petit, L. J., and others: Chronic Lymphatic Leukemia, Minnesota Med. **26**:1060, 1943.

were severe macrocytic anemia, thrombopenia and moderate leukopenia. The percentage of lymphocytes was 69, and immature forms were not present. Plasma protein determinations revealed an albumin value of 4.81, globulin of 1.62 and fibrinogen of 2.78 Gm. per hundred cubic centimeters. Autoagglutinins were demonstrated in the plasma, but there was no evidence of hemolysis. Free hydrochloric acid was found in the gastric contents. Sternal aspiration failed to reveal significant abnormalities. No enlargement of lymph nodes was noted; there was hepatomegaly, but the spleen was not palpable. The duration of symptoms was about one and one-half years. No response to treatment occurred, and the patient died two weeks after coming under observation. Necropsy revealed chronic lymphogenous leukemia without cellular immaturity but with widespread leukemic infiltration and replacement.

The frequent association of cutaneous lesions with lymphogenous leukemia is well known. Cutaneous involvement in patients with this disease may represent infiltration of leukemic cells or may be various forms of nonspecific reaction. Bäfverstedt[300] reports the case of a man aged 77 with chronic lymphogenous leukemia, who had many cutaneous tumors consisting of lymphocytes. There was no reaction of the reticulum, and the papillary layer was free from leukemic infiltration. Machacek[301] describes the case of a man of 66 years with chronic lymphogenous leukemia, whose face and upper extremities were involved by a cutaneous leukemid. A good therapeutic response was obtained from the combined use of roentgen irradiation, locally and to the whole body. Robert[302] observed a man of about 70 years who suffered with generalized cutaneous involvement, including erythroderma and pruritus. The lymph nodes were only slightly enlarged, and the liver and spleen were not palpable. The blood values were normal except for a leukocyte count of 21,000 per cubic millimeter, with 83.5 per cent of the cells lymphocytes. There was an increase of lymphocytic elements in the sternal punctate, and biopsies of the skin and of a lymph node established the diagnosis of lymphogenous leukemia. Cornell[303] reports the association in a man aged 57 of lymphogenous leukemia with a generalized cutaneous eruption, which was most pronounced on the face and extremities. The skin was edematous, erythematous and thickened. There were also many papular

300. Bäfverstedt, B.: Fall von leukämischer Lymphadenosis mit Hauttumoren, Acta dermat.-venereol. 23:591, 1943.

301. Machacek, G. F.: Chronic Lymphatic Leukemia (Cutaneous Leukemid), Arch. Dermat. & Syph. 48:671 (Dec.) 1943.

302. Robert, P.: Lymphadenosis cutis universalis (lymphatisch-leukämische Erythrodermie), Dermatologica 86:241, 1942.

303. Cornell, V. A.: Leukemia Cutis, Arch. Dermat. & Syph. 49:75 (Jan.) 1944.

lesions consisting of leukemic infiltrations.   Hansen [304] observed a man of 66 years with lymphogenous leukemia complicated by eczema pityroides.   An unusual case is described by MacKee,[305] in which a man aged 68 had a leukocyte count of 64,000 per cubic millimeter but the differential formula was stated to be normal except for 7 per cent eosinophils.   The patient had bullous cutaneous lesions, and the histologic picture presented by sections of these lesions was said to establish the diagnosis of lymphogenous leukemia.   Cannon [306] reports the incidental discovery of chronic lymphogenous leukemia in a man of 34 years who was being treated for syphilis in the secondary stage. Weintrob [307] observed a red "paint splash" appearance of the cervix of a girl of 15 years in whom later manifestations developed leading to the diagnosis of acute lymphogenous leukemia.   According to the author, this appearance of the cervix is similar to the "paint splash" appearance of the rectal mucosa of patients with leukemia described earlier by Felsen, and he believes that it may be an important early sign in leukemia.

The case of a woman of 62 years with chronic lymphogenous leukemia complicated by leukemic infiltration in the marrow spaces of the fenestral layer within the bony capsule of the inner ear is reported by Brunner.[308] There was no involvement of the endosteal or endochondral layers. Scott and Lissimore [309] report the case of a man aged 62 who suffered with chronic lymphogenous leukemia complicated by multiple attacks of mesenteric thrombosis culminating in intestinal obstruction. Treatment by irradiation and the administration of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) was successful in preventing recurrence during a three and one-half month period of subsequent observation.

Falkenstein and Fowler [310] analyze the observations in 61 cases of acute lymphogenous leukemia occurring in children under 16 years of age.   The incidence of leukemic and of subleukemic blood pictures were approximately equal.   The course of the disease in patients with

304. Hansen, P.:   Lymphatic Leukemia: Eczema Pityroides, Acta dermat.-venereol. **23**:364, 1942.

305. MacKee, G. M.:   Lymphatic Leukemia with Bullous Lesions, Arch. Dermat. & Syph. **50**:143 (Aug.) 1944.

306. Cannon, A. B.:   Primary and Secondary Syphilis: Chronic Lymphatic Leukemia, Arch. Dermat. & Syph. **49**:145 (Feb.) 1944.

307. Weintrob, M.:   Paint-Splash Cervix in Leukemia, J. Internat. Coll. Surgeons **7**:98, 1944.

308. Brunner, H.:   Changes of the Temporal Bone in Leukemia and Osteitis Fibrosa, Arch. Otolaryng. **39**: 1 (Jan.) 1944.

309. Scott, R. A. M., and Lissimore, N.:   Mesenteric Thromboses in Lymphatic Leukaemia Treated with Dicoumarol, Lancet **2**:405, 1944.

310. Falkenstein, D., and Fowler, W. M.:   Acute Lymphatic Leukemia in Childhood, Am. J. Dis. Child. **65**:445 (March) 1943.

leukemic leukocyte levels was generally more acute than that in children whose leukocyte counts were not abnormally high. It was concluded that roentgen therapy may be of value in relieving symptoms due to pressure of enlarged nodes but that it is valueless or actually harmful when employed in the absence of such symptoms.

Changes in bones revealed by roentgen examination of 7 children with leukemia are described by Soto.[311] In 6 of the patients localized rarefaction of. the metaphysis of long bones was observed. One had generalized osteoporosis.

Drummond [312] observed reduction in the size of the spleen and lymph nodes of a boy 14 years old with acute lymphogenous leukemia after the subcutaneous injection of 2 minims (0.12 cc.) of T.A.B. stock vaccine (bacterial vaccine made from the typhoid bacillus and the paratyphoid A and B bacilli). However, no effect was noted on the degree of anemia, the leukocyte level or the clinical course of the disease.

The case of a man of 36 years with typical myelogenous leukemia is reported by Heinle and Weir.[313] The diagnosis of leukemia was made in January 1935. Roentgen therapy was employed, and thyroidectomy was performed. Arsenic in the form of solution of potassium arsenite was administered with favorable effect. Three courses of roentgen therapy were given over three and one-half years. Five months before the patient's death pleurisy with effusion developed, which was proved to be of tuberculous cause. During. the final four weeks of the illness the leukocyte count decreased to normal and then to subnormal levels. The percentage of immature cells was reduced, but some evidences of immaturity persisted until his death. At necropsy miliary tuberculosis was found. Bone marrow obtained from many sites revealed only myeloid hyperplasia and metaplasia. There was no evidence of leukemic infiltration in other organs, including the spleen, which weighed 910 Gm.

The case of a man of 50 years with acute myeloblastic leukemia and rapidly progressive tuberculosis of the bronchial lymph nodes, liver and spleen is reported by Feuchtinger.[314] He comments on the difficulty of differentiating between leukemoid reactions and true leukemia in patients with active tuberculosis and states that the association of

311. Soto, J. A.: Alteraciones oséas en la leucemia del niño; estudio radiológico, Arch. de pediat. d. Uruguay **14**:415, 1943.

312. Drummond, J.: The Use of T. A. B. Vaccine in Acute Lymphatic Leukaemia, Clin. Proc. **3**:90, 1944.

313. Heinle, R. W., and Weir, D. R.: Morphologic Obliteration of Chronic Myeloid Leukemia by Active Tuberculosis: Report of a Case, Am. J. M. Sc. **207**:450, 1944.

314. Feuchtinger, O.: Tuberkulose, akute Leukämie und myeloische Reaktion, Klin. Wchnschr. **22**:669, 1943.

the two diseases has been reported rarely but that when it occurs progress of the tuberculosis is greatly accelerated.

Unusual remissions occurring in the course of subacute myelogenous (paramyeloblastic) leukemia are reported by Moeschlin.[315] In 1 of his cases there were three definite clinical and hematologic remissions, lasting seven, three and two months, respectively, before death occurred, sixteen months after the onset of the illness. In this case sternal puncture revealed proliferation of leukemic cells and normal leukopoietic elements without intermediate forms. During remission the marrow obtained by sternal puncture was completely normal. In a second case a patient with a similar form of leukemia experienced a partial remission of activity of the disease. In a third case there was temporary disappearance of cutaneous tumors and retinal infiltration. The blood and sternal punctate obtained during remission in this case revealed a considerable decrease but not complete disappearance of leukemic elements. The author concludes that in leukemia there may be either a gradual or an abrupt inhibition of maturation of all elements comprising the myeloid series. He has observed in the same patient isolated nests of cells with leukemic features and later generalized, leukemic transformation of the hemopoietic tissue. He believes that the body possesses a defense mechanism against pathologic cell development, the nature of which is obscure. The presence of abnormal cells followed by their disappearance points to the existence of some immunization process. He suggests that arsenical therapy and multiple blood transfusions may aid in the establishment of such immunization. Moeschlin states that a critical review of the literature fails to disclose a single well authenticated case in which leukemia was actually cured.

Many factors have been suggested as possible precipitating agents in the development of leukemia, especially of the more acute forms of the disease. Weiss and Haines[316] observed a Negro soldier aged 28 years who experienced severe burns from the explosion of gasoline. He received treatment in the form of blood plasma and sulfadiazine and improved until the eighth day after his injury. On the ninth day abnormal blood values were discovered, and the subsequent course of his illness was progressively unfavorable until his death, on the thirteenth day of his illness. The maximum leukocyte count was 137,800 per cubic millimeter, of which myeloblasts constituted 9 per cent, premyelocytes 4 per cent and myelocytes 4 per cent. Seventy-six per cent of the cells of the bone marrow were myeloblasts. The authors

315. Moeschlin, S.: Subakute paramyeloblasten Leukämien mit mehrfachen längeren Remissionen, Deutsches Arch. f. klin. Med. **191**:213, 1943.

316. Weiss, D., and Haines, K. E.: Burn Trauma Precipitating Acute Leukemia or a Leukemoid Condition, Am. J. M. Sc. **208**:490, 1944.

suggest that the burns may have been responsible for the development of leukemia in this case.

A man of 52 years, whose case is reported by Gerbis,[317] received roentgen therapy for dermatitis caused by turpentine. The lesions extended over the hands, arms and neck, and treatment was given for a period of three weeks. About two weeks after its discontinuance the patient first noted weakness. Approximately two months later examination of the blood led to the diagnosis of aplastic anemia. Death occurred four months after the termination of irradiation therapy, and necropsy revealed the presence of subleukemic myelogenous leukemia. Rachner[318] reports the case of a 33 year old man who had been a vulcanizer for nineteen years. He suffered with chronic benzene intoxication, and his illness terminated in acute myelogenous, leukemia. The diagnosis made at necropsy was chloroleukemia. In this case leukemia was considered an occupational disease.

An unusual case of myelogenous leukemia associated with hypertension and heart block in a woman aged 64 is reported by Blotner and Sosman.[319] On two occasions, but not on a third, roentgen irradiation over the heart caused the 2:1 heart block to disappear for several days. The authors suggest, without histologic evidence, that the block was due to leukemic infiltration of the bundle of His.

Case reports of monocytic leukemia characterized by ulcerating and necrotic lesions of the oral and nasal mucous membranes are reported by Aseltine,[320] Leocádio,[321] Boyd-Cooper,[322] Hatch,[323] Dodge, Black and Mugrage[324] and Sacks.[325] Subleukemic monocytic leukemia and aleukemic reticuloendotheliosis with cutaneous involvement are the subjects of case reports by Smith and his associates [326] and by Michelson.[327]

317. Gerbis, H.: Aleukemische Myelose nach therapeutischer Röntgenbestrahlung der Haut, Deutsche med. Wchnschr. **69**:540, 1943.

318. Rachner, H.: Chloroleukämie als Folge einer Benzolvergiftung, Deutsche med. Wchnschr. **70**:219, 1944.

319. Blotner, H., and Sosman, M. C.: X-Ray Therapy of the Heart in a Patient with Leukemia, Heart Block and Hypertension: Report of a Case, New England J. Med. **230**:793, 1944.

320. Aseltine, L. F.: Monocytic Leukemia with Oral Manifestations: Report. of Case, J. Oral Surg. **2**:266, 1944.

321. Leocádio, J.: Leucemia monocitica, Brasil-med. **58**:83, 1944.

322. Boyd-Cooper, B.: Ulcerative Stomatitis in a Case of Subacute Monocytic Leukaemia, Brit. Dent. J. **76**:1, 1944.

323. Hatch, F. N.: Leukemia as a Cause of Nasal Obstruction: Report of a Case, California & West. Med. **61**:23, 1944.

324. Dodge, H. J.; Black, W. C., and Mugrage, E. R.: Acute Monocytic Leukemia: Case Report, Rocky Mountain M. J. **41**:177, 1944.

325. Sacks, I.: A Case of Acute Monocytic Leukemia, South African M. J. **18**:248, 1944.

Failure to recognize the presence of acute leukemia in a patient receiving treatment for Vincent's infection of the mouth is illustrated by a case reported by Cahn.[328]

Rapid progress of leukemia in a soldier 19 years of age is reported by Julliard and Blancardi.[329] The duration of the illness was five days, and the symptoms were fever, diarrhea and hemorrhagic manifestations. Necropsy revealed replacement of normal myeloid elements by abnormal leukoblasts, with infiltration of the spleen and lymph nodes by leukemic cells classified as myeloblasts.

The subject of acute leukemia is reviewed by Ducach Grinberg[330] in a monograph. Eighteen cases observed by the author are discussed in detail. The literature referred to in ▲this article is predominantly European.

Pérez Díaz and de la Huerta[331] report the case of a 59 year old woman with a history of jaundice of eight months' duration. The diagnosis of acute subleukemic hemocytoblastic leukemia was made by sternal aspiration. The enlarged liver contained nodules consisting of the same type of cells as those found in the marrow. López Fernández and Bidot Peralta[332] observed a youth of 18 with symptoms and signs suggestive of tuberculous peritonitis. The blood picture when the patient was first seen was not suggestive of leukemia, but the ascitic fluid contained leukemic cells. Later examination of the blood revealed the features of acute hemocytoblastic leukemia.

A case of eosinophilic leukemia in a Negro boy of 11 years is reported by Friedman, Wolman and Tyner.[333] Although the course of the disease was rapid, with death occurring approximately five months after the onset of symptoms, the cells in the peripheral blood were nearly all mature forms. The maximum total leukocyte count was 194,000 per cubic millimeter, and the percentage of eosinophils

326. Smith, D. C.; Shafer, J. C.; Jones, P. E.; Crutchfield, A. J., and Booker, P.: Monocytic Leukemia Cutis, Arch. Dermat. & Syph. **50**:132 (Aug.) 1944.

327. Michelson, H. E.: Aleukemic Reticuloendotheliosis, Arch. Dermat. & Syph. **48**:683 (Dec.) 1943.

328. Cahn, L. R.: Necessity for Pre-Operative Investigation: Report of Case of Acute Myeloblastic Leukemia, Ann. Dent. **2**:108, 1943.

329. Julliard, J., and Blancardi, C.: Leucose aiguë leucopénique et syndrome hémogeno-hémophilique terminal, Presse méd. **50**:53, 1942.

330. Ducach Grinberg, G.: La leucemia de celulas primitivas, Chile, Impr. Univ. Santiago, 1939.

331. Pérez Díaz, R., and de la Huerta, R.: Sobre un caso de leucemia hemocitoblástica a forma ictero-hepática, Rev. méd. cubana **55**:589, 1944.

332. López Fernández, F., and Bidot Peralta, C.: Leucemia aguda hemocitoblástica a forma de ascites hemorrágica, Rev. méd. cubana **54**:560, 1943.

333. Friedman, M.; Wolman, I. J., and Tyner, H. H.: Eosinophil Leukemia with Report of a Case, Am. J. M. Sc. **208**:333, 1944.

ranged between 80 and 90. The authors review 12 other reported cases of eosinophilic leukemia. All occurred in males. The age of the patients, clinical manifestations and rapidity of progress of the disease were extremely variable. Norcross and others [334] report a case of plasma cell leukemia in a man of 73 years. Kopač [335] reports the case of a man aged 51 for whom a clinical diagnosis of aleukemic myelogenous leukemia had been made. Necropsy revealed proliferating megakaryocytes associated with myelocytes and erythroblasts within the spleen. Rather unjustifiably, it appears, the case is classified as one of megakaryocytic leukemia.

Instances of pregnancy in women suffering with leukemia are reported by van der Sar and Hartz,[336] Hochman [337] and Angelucci.[338] Hochman, who observed 2 cases, both of chronic myelogenous leukemia, in 1 of which pregnancy was interrupted and in the other of which the woman was allowed to go to term and delivered a normal child, concludes that pregnancy will neither shorten the life of the mother nor result in a leukemic child. With the latter statement there is general agreement, but it is the consensus of most observers that pregnancy has a distinctly unfavorable effect on the course of chronic leukemia.

Henshaw and Hawkins [339] compared the incidence of leukemia among physicians with that recorded for the general population, obtaining their data from the obituary lists published in *The Journal of the American Medical Association,* the mortality reports of the United States Bureau of the Census and an unpublished compilation of the United States Public Health Service. They found that leukemia was recognized 1.7 times more frequently among physicians than among white males in the general population. They suggest that exposure to roentgen rays may be responsible for the increased incidence of leukemia among physicians, although they admit that no direct proof exists that roentgen radiation acts to incite leukemia in human beings.

334. Norcross, J. W.; Holmes, G. W., and others: Plasma-Cell Leukemia, with Involvement of Bone Marrow, Spleen, Lymph Nodes, Esophagus, Lungs and Kidneys: Clinicopathological Exercise, New England J. Med. **229**:1011, 1943.

335. Kopač, Z.: Ueber die Bedeutung der Megakaryocytenleukämien, Virchows Arch. f. path. Anat. **310**:660, 1943.

336. van der Sar, A., and Hartz, P. H.: Leucemia y embarazo, Rev. Policlín. Caracas **12**:325, 1943.

337. Hochman, A.: Leukaemia and Pregnancy, J. Obst. & Gynaec. Brit. Emp. **51**:231, 1944.

338. Angelucci, H. M.: Myelogenous Leucemia Complicating Pregnancy, Am. J. Obst. & Gynec. **48**:125, 1944.

339. Henshaw, P. S., and Hawkins, J. W.: Incidence of Leukemia in Physicians, J. Nat. Cancer Inst. **4**:339, 1944.

Leukemia in domestic animals is the subject of contributions by Stonebraker,[340] Fortner [341] and Lee.[342]

Experimental Studies on Leukemia.—Differences, both qualitative and quantitative, were observed by Abels and his colleagues [343] in the utilization of pyruvate by normal and leukemic white blood cells. They found that normal cells apparently utilize less pyruvate and, in most instances, convert a greater proportion of that compound to lactate than do leukemic cells. This abnormal behavior of the neoplastic cells is not due simply to their apparent immaturity. No explanation of the inability of leukemic leukocytes to metabolize thiamine normally is offered, and what other substances may be formed by the pyruvate and by the leukemic cells are not known.

The effect of removal of various endocrine glands on the incidence of spontaneous leukemia in a susceptible strain of mice was investigated by McEndy, Boon and Furth.[344] When the thymus was removed, the percentage of animals in which leukemia developed decreased from 77 to 8 among females and from 61 to 11 among males. A lowering of the incidence of leukemia also followed ovariectomy or orchidectomy. Removal of the spleen when the animals were 28 to 48 days of age failed to influence the incidence of leukemia. In animals not operated on leukemia occurred more frequently among females than among males. White, Mider and Heston [345] found that when a diet low in cystine was fed to mice of a strain susceptible to leukemia, induced by painting with methylcholanthrene, the incidence of the disease was only 10 per cent, whereas in 90 per cent of animals receiving the same diet with cystine added leukemia developed. The incidence of leukemia was not affected by altering the lysine content of the diet; but addition of methionine to a low cystine diet increased the occurrence of the disease to the same extent as did the addition of cystine. The data suggested to the author that cystine played a role in the development of induced leukemia, perhaps associated not with its properties as an amino acid essential for growth but with some other undetermined property.

340. Stonebraker, K.: Lymphocytomatosis in a Young Calf, Vet. Med. **39**: 316, 1944.

341. Fortner, J.: Untersuchungen über die Rinderleukose, Ztschr. f. Infektionskr. **60**:215, 1944.

342. Lee, C. D.: Clinical Manifestations of Avian Leukosis, North Am. Vet. **24**:670, 1943.

343. Abels, J. C.; Jones, F. L.; Craver, L. F., and Rhoads, C. P.: Metabolism of Pyruvate by Normal and Leukemic White Cells, Cancer Research **4**:149, 1944.

344. McEndy, D. P.; Boon, M. C., and Furth, J.: On the Role of Thymus, Spleen, and Gonads in the Development of Leukemia in a High-Leukemia Stock of Mice, Cancer Research **4**:377, 1944.

345. White, J.; Mider, G. B., and Heston, W. E.: Effect of Amino Acids on Induction of Leukemia in Mice, J. Nat. Cancer Inst. **4**:409, 1944.

Kaplan and Kirschbaum [346] were unable to increase the incidence or hasten the time of onset of methylcholanthrene-induced leukemia by means of roentgen irradiation, employing both DBA and F strains of mice. Kirschbaum [347] studied the latter strain with respect to genetic and nongenetic factors which had a bearing on the development of leukemia.

A paradoxic effect of the administration of a carcinogenic hydrocarbon on the development of transplanted leukemia in mice is reported by Stamer [348] and by Stamer and Engelbreth-Holm.[349] They found that 9,10-dimethyl-1,2-benzanthracene when injected into mice either by intravenous or intraperitoneal routes was able to inhibit and also to cure transplanted leukemia when the substance was given in sufficiently large amounts and over a protracted period.

The growth of transplanted lymphosarcoma in rats is inhibited by the local actions of gastric mucin, according to Williams.[350] The effect was attributed to an augmentation of the local foreign body and inflammatory process to such a degree that the neoplastic cells were destroyed. In the peritoneal cavity the reaction was not sufficient to prevent effectively the growth of the transplanted tumor cells.

The susceptibility influence promoting the growth of transplantable leukemia in certain susceptible strains of mice is transmitted in the milk throughout the lactation period, according to Law.[351] By this means he was able to obtain growth of two transplantable lymphoid leukemias and one myeloid leukemia in normally refractory mice. Saline extracts prepared from homogenized liver, spleen or mammary gland were found to contain the susceptibility influence of myeloid leukemia, line C1498. This susceptibility influence possessed the following characteristics:

346. Kaplan, H. S., and Kirschbaum, A.: Studies on Synergism of Leukemogenic Agents in Mice, Proc. Soc. Exper. Biol. & Med. **55:**262, 1944.

347. Kirschbaum, A.: Genetic and Certain Non-Genetic Factors with Reference to Leukemia in the F Strain of Mice, Proc. Soc. Exper. Biol. & Med. **55:**147, 1944.

348. Stamer, S.: Effect of a Carcinogenic Hydrocarbon on Manifest Malignant Tumors in Mice: Eradication of Transplanted Leukemia in Mice and Attempts at Inhibition of Other Manifest Malignant Tumors in Mice by Treatment with 9 : 10-Dimethyl-1 : 2-Benzanthracene, Acta path. et microbiol. Scandinav., 1943, supp. 47, p. 1.

349. Stamer, S., and Engelbreth-Holm, J.: Influence of Carcinogenic Hydrocarbon upon Transplanted Leukemia, Acta path. et microbiol. Scandinav. **20:**360, 1943.

350. Williams, W. L.: The Effects of Gastric Mucin on the Growth of Transplanted Tumor (Lymphosarcoma) Cells in Mice, Yale J. Biol. & Med. **17:** 311, 1944.

351. Law, L. W.: Characterization of Influence Affecting Growth of Transplantable Leukemias in Mice, Cancer Research **4:**257, 1944.

1. It underwent dialysis through parchment paper at — 4 C.

2. It remained stable in a 50 per cent solution of glycerin for thirty days at — 4 C.

3. Stability was retained after heating at 85 C. for twenty minutes.

4. It passed through a Seitz filter, with some loss.

5. It apparently was not inactivated by partial digestion.

Murphy and Sturm [352] found that adrenalectomy increased the susceptibility of rats to transplantable lymphatic leukemia. This particular leukemia was characterized by extension of the thymus, an organ which is stimulated, even in older animals, by removal of the adrenals. The authors advance the hypothesis that hormones influencing lymph tissue play a role in malignant conditions affecting this tissue. In a later communication the same authors [353] state that when adrenal cortex extracts, including desoxycorticosterone and a pituitary adrenotropic hormone, are given to a susceptible strain of rats the resistance of the animals to a transplantable lymphatic leukemia is increased.

While studying the effects of transplantable leukemia in rats, Sturm [354] observed that whole plasma obtained from normal and from leukemic animals showed little difference in prothrombin time, as determined by the method of Quick. When, however, the plasma was diluted, the prothrombin time of the leukemic rats was greatly prolonged in comparison to that of the normal animals. Extensive infiltration of the liver and spontaneous hemorrhages were characteristic of the rats with leukemia.

Engelbreth-Holm and Eltorm [355] demonstrated that leukemia cells in mice were distinctly more sensitive than normal cells to lowering of the body temperature.

Attempts by Thiersch [356] to transmit leukemia of human beings and of mice to chick embryos and to young chicks were unsuccessful.

Polycythemia.—The treatment of polycythemia by means of roentgen irradiation is discussed by Lahm.[357] He reports the results of such

352. Murphy, J. B., and Sturm, E.: Adrenals and Susceptibility to Transplanted Leukemia of Rats, Science **98**:568, 1943.

353. Murphy, J. B., and Sturm, E.: The Effect of Adrenal Cortical and Pituitary Adrenotropic Hormones on Transplanted Leukemia in Rats, Science **99**:303, 1944.

354. Sturm, E.: The Prothrombin Concentration in the Plasma of Normal and Leukemic Rats, Cancer Research **4**:35, 1944.

355. Engelbreth-Holm, J., and Eltorm, H.: Effect of Leukemia in Mice from Lowering of Body Temperature, Acta path. et microbiol. Scandinav. **20**: 346, 1943.

356. Thiersch, J. B.: Attempts to Transmit Leucaemia of Man and of Mice to Chick Embryo and to Young Chick by Amniotic and Intravenous Routes, Australian J. Exper. Biol. & M. Sc. **22**:57, 1944.

therapy for 12 patients who were under observation for ten years. Nine of his patients were men and 3 were women. No undesirable complications occurred in 10; 1 acquired myelogenous leukemia, and in another severe anemia developed which was thought to be due to an excessive irradiation effect since his blood values later became normal and he remained in comparatively good health. Lahm advocates treatment over all the bones rather than locally over the spleen but does not mention the use of "spray" irradiation of the whole body. He employs a total dose of 2,340 r given during a period of thirty-five to forty-eight days. The importance of differentiating between true and secondary polycythemia is emphasized. Von Jagić[358] describes the diagnostic features presented by the common anemias and polycythemia and discusses the forms of therapy available for these conditions. In the management of patients with polycythemia he recommends venesection and the administration of phenylhydrazine, reserving the use of roentgen irradiation over the long bones for severely ill patients.

A case of polycythemia occurring in a member of a family in which other members were believed to be similarly affected is reported by Laszlo and Geroefy.[359] The disease was apparently transmitted by the father to three of seven children. Glazebrook[360] reports the case of a woman aged 56 who presented the feature of koilonychia, or spoon nails, associated with polycythemia. Treatment by irradiation of the whole body was successful in controlling the polycythemia, and the abnormality of the nails disappeared. Marshall[361] reports the successful extraction of bilateral cataracts from a man of 74 years with polycythemia. Excellent colored illustrations of the ocular fundi as they appear in patients with polycythemia are included in this article. Stanton and Scharf[362] observed a man aged 47 with polycythemia complicated by hypertension and dementia precox.

To determine the effects of elevation of the erythrocyte count on tolerance to deprivation of oxygen, Wetzig and D'Amour[363] induced

357. Lahm, W.: Ueber die Röntgenbehandlung der Polyzythämie, Strahlentherapie **73**:306, 1943.

358. von Jagić, N.: Zur Klinik und Therapie der Anämien und Polyglobulien, Wien. klin. Wchnschr. **56**:59, 1943.

359. Laszlo, G., and Geroefy, K.: Ein hereditärer Fall von Polycythaemia rubra, Folia haemat. **67**:316, 1943.

360. Glazebrook, A. J.: Koilonychia and Polycythaemia Vera, Edinburgh M. J. **51**:65, 1944.

361. Marshall, J. C.: A Case of Polycythaemia Vera: Extraction of Both Lenses; Satisfactory Result, Brit. J. Ophth. **28**:481, 1944.

362. Stanton, J., and Scharf, L. E.: Polycythemia Vera Rubra (Erythremia), M. Bull. Vet. Admin. **20**:453, 1944.

363. Wetzig, P., and D'Amour, F. E.: Effects of Polycythemia and of Carrot Diet on Resistance to Anoxia, Am. J. Physiol. **140**:304, 1943.

polycythemia in rats and found no change in their resistance to anoxia when the erythrocyte count was increased by 24 per cent or 56 per cent.

Multiple Myeloma.—A review article dealing with the origin and function of plasma cells and containing an extensive bibliography was published in 1941 by Fleischhacker.[364]   He discusses the anatomy, embryology, development and classification of reticulum cells and plasma cells of the bone marrow. Plasma cells, he believes, arise from undifferentiated reticulum or stem cells of the marrow. The relation of the plasma cells to multiple myeloma is considered, and the classic features of the disease are enumerated.

Blackman and his associates[365] report the case of a man aged 45 with multiple myeloma, on whom extensive studies of the serum proteins and urinary proteins were made. The Bence-Jones protein behaved like a globulin. Electrophoretically it moved as a beta globulin. It was present in increased amounts in the plasma and was believed responsible for ultimate renal failure through precipitation in the renal tubules. Harvier and Rangier[366] found large amounts of Bence-Jones protein in the urine of a patient with primary carcinoma of the kidney and extensive metastases to the bones. The protein was isolated and studied chemically. It did not appear to be either an albumose or a globulin. Its presence was attributed to the destruction of bone.

The diagnosis of multiple myeloma is discussed by Ley and Roca de Viñals,[367] who report a case. The most important diagnostic features are believed to be the elevation of the serum proteins and the characteristic changes in the marrow. Leypold[368] reports the case of a man of 46 years with multiple myeloma and terminal uremia. The blood level of cholesterol was decreased to 96 mg. per hundred cubic centimeters, and the author suggests that hypocholesteremia may be a characteristic feature of this disease. Heidenström and Tottie[369] describe a case of multiple myeloma in a man aged 39, in which the disease was complicated by extensive cutaneous and articular

364. Fleischhacker, H.: Ueber die Bedeutung der Reticuloendothelien und Plasmazellen des Knochenmarkes, Ergebn. d. inn. Med. u. Kinderh. **60**:508, 1941.

365. Blackman, S. S., Jr.; Barker, W. H.; Buell, M. V., and Davis, B. D.: On the Pathogenesis of Renal Failure Associated with Multiple Myeloma: Electrophoretic and Chemical Analysis of Protein in Urine and Blood Serum, J. Clin. Investigation **23**:163, 1944.

366. Harvier, P., and Rangier, M.: Caractères chimiques de l'albumine de Bence-Jones, Compt. rend. Acad. d. sc. **216**:131, 1943.

367. Ley, E., and Roca de Viñals, J.: Contribución al estudio clínico de los mielomas múltiples, Rev. clín. españ. **10**:86, 1943.

368. Leypold, F.: Zur klinischen Diagnostik des Myeloms (Plasmozytom), Deutsche med. Wchnschr. **70**:36, 1944.

369. Heidenström, N., and Tottie, M.: · Haut- und Gelenkveränderungen bei multiplem Myelom, Acta dermat.-venereol. **24**:192, 1943.

involvement. Newns and Edwards [370] observed a woman of 45 years with multiple myeloma associated with renal and widespread subcutaneous metastases. Wolff and Nolan [371] report the case of a Negro woman of 44 years, believed to be the first recorded of multiple myeloma originating in the mandible. Brehant [372] reports the occurrence of a solitary plasmocytoma in the tibia of a man aged 66. Bence-Jones protein was demonstrated in the urine. The case is considered unusual because of the age of the patient. It is stated that solitary plasmocytoma is, as a rule, seen only in young adults. Gordon and Walker [373] observed a woman of 30 years with a plasmocytoma of the upper lobe of the left lung. The site of origin of the tumor was undetermined. Rubinstein [374] reports the case of a boy who began to have pain in the left hip at the age of 12 years, ultimately suffering a pathologic fracture. The diagnosis of multiple myeloma was made by sternal aspiration when he was 15 years old. Changes in the plasma proteins and the appearance of Bence-Jones protein in the urine did not occur until later. Keefer and others [375] describe the case of a man aged 56 years with plasma cell myeloma of the liver and bone marrow. The clinical diagnosis had been cirrhosis of the liver. Hernández Morales [376] reports a case of multiple myeloma in a 50 year old Puerto Rican man, in which 65 per cent of the sternal marrow cells consisted of plasmablasts and plasmacytes.

370. Newns, G. R., and Edwards, J. L.: A Case of Plasma Cell Myelomatosis with a Large Renal Metastasis and Widespread Renal Tubular Obstruction, J. Path. & Bact. 56:259, 1944.

371. Wolff, E., and Nolan, L. E.: Multiple Myeloma First Discovered in the Mandible, Radiology 42:76, 1944.

372. Brehant, M.: Plasmocytome solitaire du tibia, J. de chir. 58:98, 1941-1942.

373. Gordon, J., and Walker, G.: Plasmocytoma of the Lung, Arch. Path. 37:222 (March) 1944.

374. Rubinstein, M. A.: Multiple Myeloma in a 15 Year Old Boy, New York State J. Med. 44:2491, 1944.

375. Keefer, C. S.; Castleman, B., and others: Plasma-Cell Myeloma Involving Liver and Bone Marrow: Clinico-Pathological Exercises, New England J. Med. 230:774, 1944.

376. Hernández Morales, F.: A Case of Multiple Myeloma, Bol. Asoc. méd. de Puerto Rico 36:278, 1944.

(To Be Continued)

News and Comment

GENERAL NEWS

National Gastroenterological Association 1946 Award Contest.—The National Gastroenterological Association announces the establishment of an annual cash prize of $100 and a certificate of merit for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The award is to be made at the annual convention banquet of the National Gastroenterological Association, to be held at the Hotel Pennsylvania in New York city on Thursday evening, June 20, 1946.

All entries for the 1946 prize should be limited to five thousand words, typewritten in English, prepared in manuscript form, submitted in five copies and accompanied with an entry letter; entries must be received not later than May 1, 1946. They should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23, N. Y.

Urology Award.—The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deems none of the offerings worthy no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the Secretary for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Netherland Plaza Hotel, Cincinnati, Ohio, July 22-25, 1946.

Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis 3, Tenn., on or before July 1, 1946.

STREPTOCOCCIC AND NONSTREPTOCOCCIC DISEASE OF THE RESPIRATORY TRACT

Epidemiologic Observations

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MINNEAPOLIS

DURING the winter of 1943-1944, an extensive study of hemolytic streptococcus sore throat was conducted in a military post. Information in regard to certain aspects of the epidemiology of streptococcic and nonstreptococcic disease of the respiratory tract was obtained and deserves presentation.

The personnel of which the study group was composed changed from time to time, and precise information as to its composition from the standpoint of several of the factors to be considered here was unknown. It was not possible for this reason to determine the true incidence of disease in special groups, but a comparison could always be made between the relative .frequency of occurrence of streptococcic and nonstreptococcic inféctions. It was from this point of view that the following report was prepared.

Study Group.—The study group was the personnel of a military post located in an area in which the incidence of streptococcic disease of the respiratory tract was known to be high. Troop training was of an advanced type, and relatively few of the men had received less than three months of basic training on arrival at the post. Large units, up to and including divisions, were transferred into and out of the post during the study period.

Methods.—All patients with infections of the respiratory tract admitted to the station hospital were studied. Diseased persons were routinely hospitalized if the temperature on examination in the dispensary was greater than 100 F. A history, physical examination and culture materials from the throat were obtained by a

member of the commission. Swabs were immediately streaked on horse blood agar plates and incubated for eighteen hours at 37 C. The plates were then examined and the presence or absence of hemolytic streptococci determined. A roughly quantitative estimate of the number of organisms was established. The groups and types of the isolated hemolytic streptococci were determined by the precipitin technic of Lancefield.[1]

Disease.—For the purpose of this study the cases of disease of the respiratory tract were divided into four groups:

1. Hemolytic Streptococcus Sore Throat: Disease of the respiratory tract was assumed to be caused by hemolytic streptococci when the presence of large numbers of these organisms of the Lancefield group A were demonstrated to be present in the nose and/or throat, when the physical examination revealed exudative tonsillitis or great redness and edema of the soft tissues of the throat and especially when definite tender adenitis of the anterior cervical lymph nodes was discovered. In certain cases a scarlatiniform rash was also observed. A significant antistreptolysin and/or antifibrinolysin response occurred in 87.5 per cent of 342 of these patients for whom suitable serial determinations were made, indicating that the clinical diagnosis was usually correct.

2. Nonstreptococcic Disease: Cases of disease of the respiratory tract were included in the nonstreptococcic group if hemolytic streptococci were not recovered from the nose or throat and if the common communicable diseases appeared to be absent. Many of the patients suffered from infections associated with an influenza-like syndrome. Some had mild to severe atypical pneumonia, and others with this disease were undoubtedly given incorrect diagnoses.

3. Indeterminate Group: Two types of cases were included in this group. To the first type belonged those in which the history· and physical examination suggested a virus disease of the respiratory tract but in which group A hemolytic streptococci were recovered from the throats of the patients. The organisms were usually present in small numbers, and these cases are believed to represent other types of disease of the respiratory tract occurring in hemolytic streptococcus carriers.

A small number of persons were observed whose histories and features observed on physical examinations were similar to those obtained and observed in instances of hemolytic streptococcus sore throat, but from whose throats these organisms could not be recovered.

4. Miscellaneous: Cases of the common communicable diseases, such as measles, chickenpox and meningococcic meningitis as well as pneumococcic pneumonia, were included in a separate group.

1. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251. Precipitin typing serums were supplied in part through the courtesy of Dr. Rebecca C. Lancefield.

The description to follow. of certain aspects of disease of the respiratory tract will be confined to those of groups 1 and 2, both of which are large and represent infections in which streptococci definitely were or were not the etiologic agents.

Epidemic Dynamics.—The epidemic dynamics of acute disease of the respiratory tract within the post selected for study over a period of eighteen weeks are presented in chart 1. The incidence of all disease of the respiratory tract for the Service Command in which the post was located is also included.
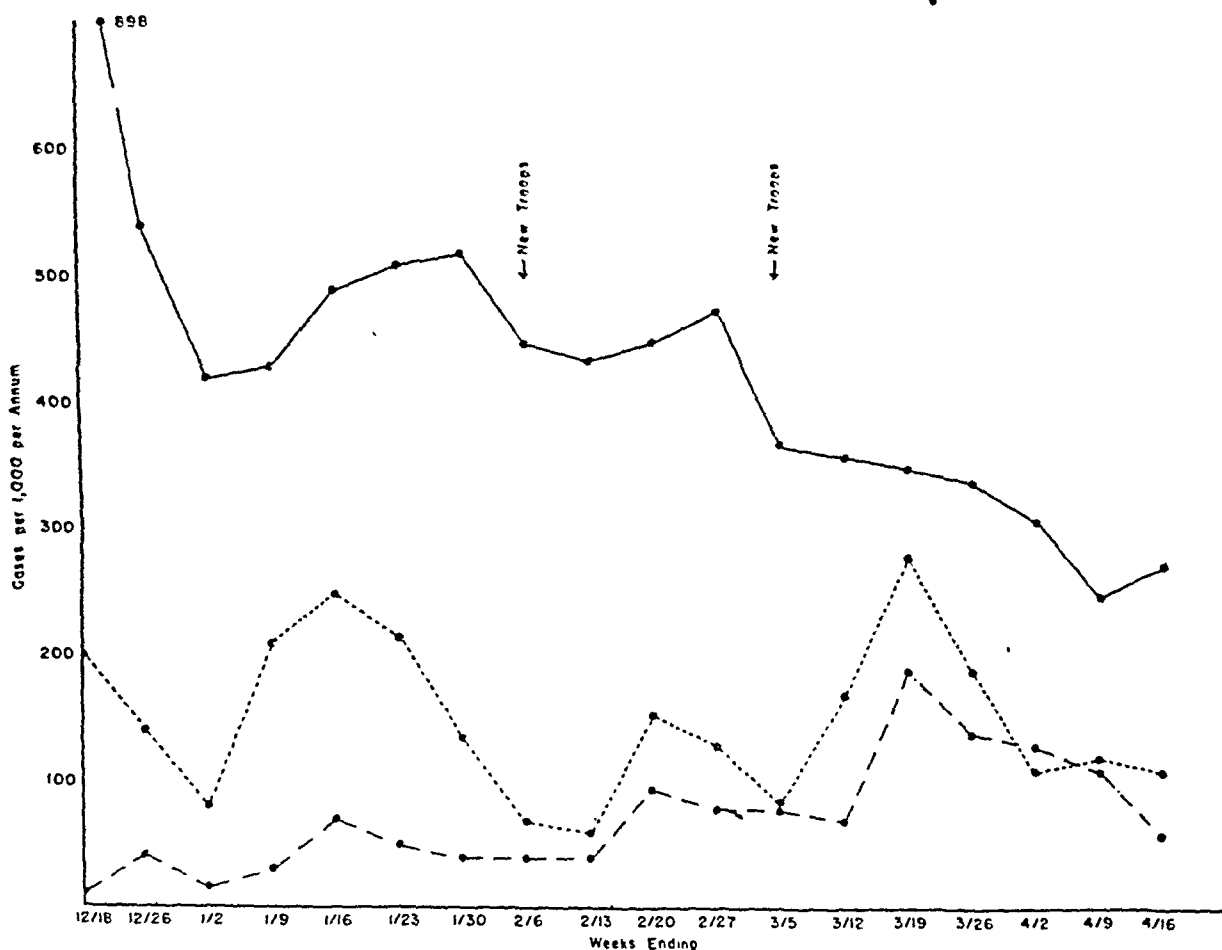

Fig. 1.—Epidemic dynamics of streptococcic and nonstreptococcic disease of the respiratory tract. The solid line indicates the incidence of disease of the respiratory tract in the entire Service Command; the dotted line indicates the incidence of nonstreptococcic disease of the respiratory tract in the post selected for study, and the broken line indicates the incidence of streptococcic disease of the respiratory tract in the post.

A sharp outbreak of influenza A, which was nationwide in its extent, is reflected in the high and rapidly declining rate for disease of the respiratory tract during the last two weeks of December. During January there was an increase in the incidence of disease of the respiratory tract in the Service Command and in the post selected for study. The

characteristic clinical illness during this time was different from that associated with infection by the influenza virus in that it was more protracted and that cough and laryngitis were severe. Neither of these outbreaks was accompanied with or followed over a period of several weeks by an increase in the frequency of occurrence of streptococcic infection. These organisms were responsible for about 25 per cent of all cases during the first six weeks of the study period. At this time nearly all the troops had been stationed in the post for six months or more.

A definite increase in the rates for both streptococcic and nonstreptococcic disease followed the transfer to the camp in the first week of February of a new regiment of seasoned troops from another area. This occurred at a time when the disease rate in the Service Command was approximately stationary and when the outbreak of January had subsided.

In the first week of March a division which had been in training for eight months in an area in which disease of the respiratory tract was rarely observed was transferred to the post. This event was followed immediately by an increase in the frequency of occurrence of nonstreptococcic and, one week later, of streptococcic infection. At the height of the outbreak, which was reached in about two weeks, the infections in 40 to 50 per cent of all cases were caused by streptococci. Four weeks after the influx of new troops the incidence of disease was again low.

Streptococcic Types.—In table 1 the frequency with which each type of streptococcus was involved in the causation of disease is presented.

TABLE 1.—*Distribution of Serologic Types in Cases of Hemolytic Streptococcus Sore Throat*

	Number of Cases		Number of Cases
Not group A	25	Type 18	3
Untypable	59	Type 19	56
Type 1	12	Type 22	1
Type 3	39	Type 24	10
Type 4	1	Type 26	9
Type 5	5	Type 30	24
Type 6	13	Type 32	1
Type 8	2	Type 36	69
Type 9	2	Type 40	1
Type 12	2	Type 41	2
Type 13	1	Type 43	1
Type 14	3	Type 44	9
Type 17	27	Type 46	14

Untypable strains and strains of only thirteen types were responsible for 95 per cent of all streptococcic infections, and the five most common types, ·3, 17, 19, 30 and 36, for 57 per cent.

In chart 2 the actual number of infections by any type in 2 or more cases in a week are presented. This chart clearly shows that a true monotype epidemic was never established. During the outbreak in the final month, seven to nine types caused infections in 2 or more cases each

week and from 15 to 25 per cent of the infections were due to the less frequently occurring types.

In January and February, types 3, 17, 19 and 36 were isolated most frequently and types 6 and 44 were not uncommon. Type 30 appeared for the first time in February after a large unit of new troops entered the post. Types 1, 24 and 26 became established with the second influx
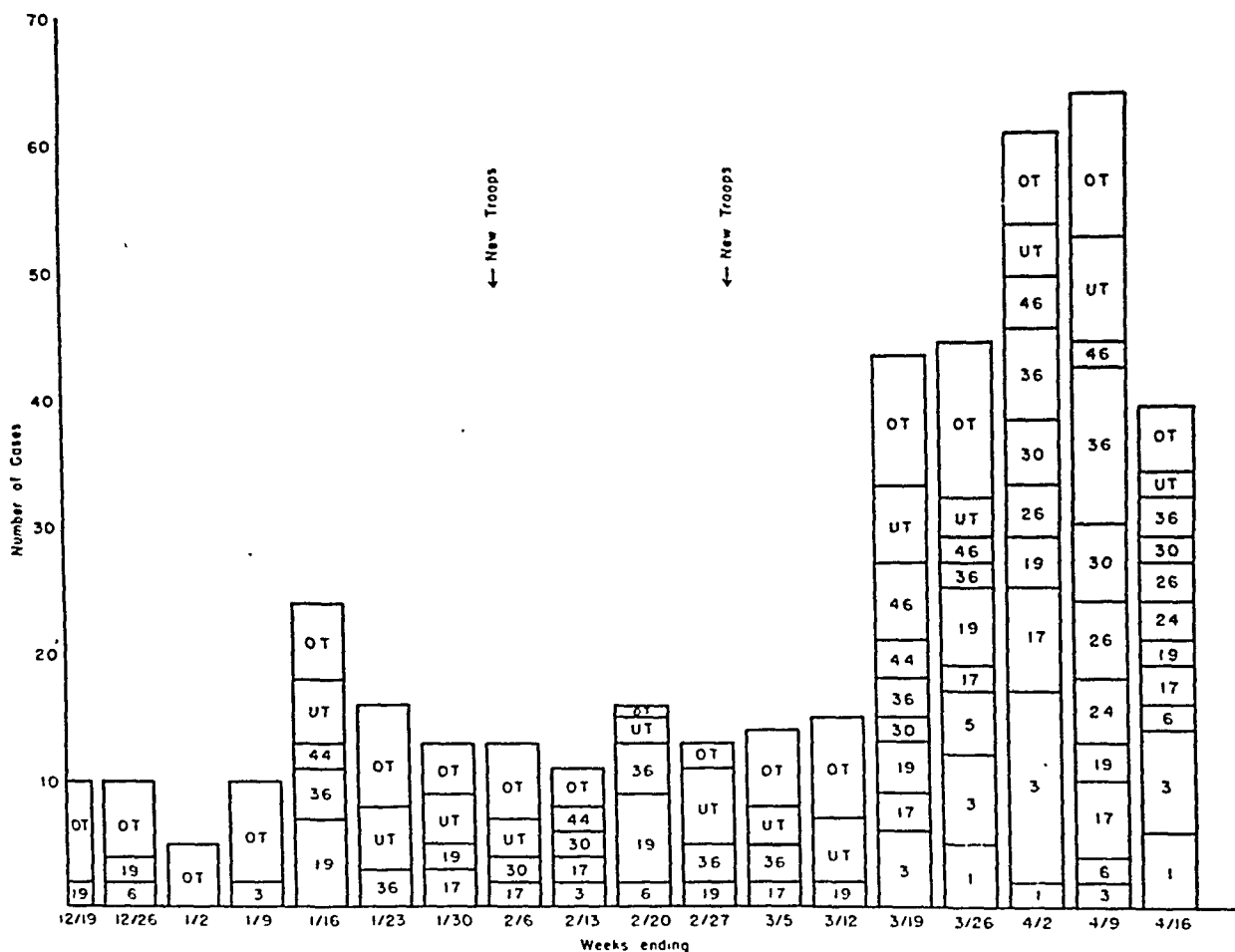

Fig. 2.—Weekly distribution of cases of group A hemolytic streptococcus infection of the respiratory tract by serologic types. *OT* indicates other types; *UT*, untypable.

of troops, in March, but caused relatively little disease. Throughout the study period the strains of the five most common types were the predominating infectious agents.

In one week, 5 cases of infection with type 5 were discovered, and it is of interest to note that the men with these infections had no known contact with one another so far as their military activities were concerned.

Duration of Military Service.—The duration of military service of the members of the total study group was not known, but nearly all the troops had had more than six months of training. This fact is

reflected in the data presented in table 2. Only 10 to 15 per cent of the men suffering from acute illnesses of the respiratory tract had been less than six months in the army, and approximately 50 per cent had been in more than twelve months.

TABLE 2.—*Relation of the Duration of Military Service to the Incidence of Streptococcic and Nonstreptococcic Disease of the Respiratory Tract*

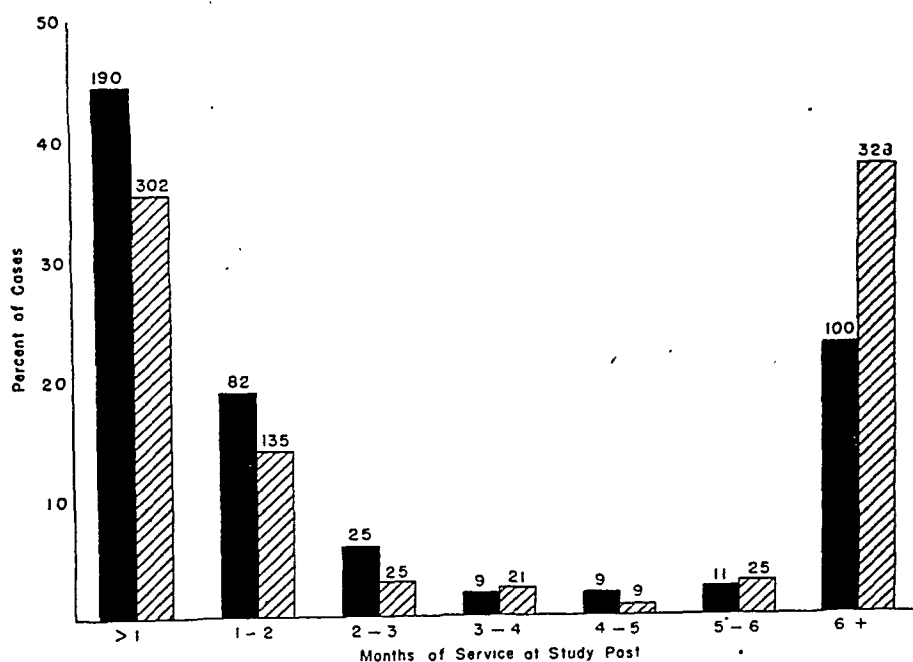|	Nonstreptococcic Disease		Streptococcic Disease	
	Number	Per Cent	Number	Per Cent
0 to 1 month	14	1.7	3	0.7
1 to 3 months	50	5.9	28	6.6
4 to 6 months	56	6.6	11	2.6
7 to 9 months	223	27.4	95	22.5
10 to 12 months	75	8.9	53	12.5
13 to 18 months	174	20.6	122	28.9
19 to 24 months	77	9.1	39	9.2
24 months and up	176	20.8	71	16.8
Total number of cases.	845		422	

Fig. 3.—Relation between the duration of service in the post selected for study and the incidence of streptococcic and nonstreptococcic disease of the respiratory tract. The solid columns indicate streptococcic disease; the shaded columns, nonstreptococcic disease.

It is also clear that a striking parallelism existed between streptococcic and nonstreptococcic disease in that neither was more likely to occur in men of short military service and that both appeared with about equal frequency in groups with various durations of service.

Duration of Service in Post Selected for Study.—A definite correlation was established between the incidence of disease of the respiratory tract and the length of service at the post selected for study, in contrast to the failure to demonstrate such a relation for the total duration of military service. Chart 3 illustrates this fact. Forty-four and six-tenths per cent of streptococcic infections and 35.8 per cent of nonstreptococcic infections occurred among men who had been in residence in the post for less than one month, and 63.8 per cent and 51.8 per cent, respectively, among those in residence for less than two months.

In this regard it should be borne in mind that approximately 25 per cent of the total cases of streptococcic disease. but 50 per cent of the cases of nonstreptococcic disease. occurred during the first nine weeks of the study, during which time the largest part of the personnel of the post was composed of men who had been stationed there for more than six months.

TABLE 3.—*Relation of Age to the Incidence of Streptococcic and Nonstreptococcic Disease of the Respiratory Tract*

Age	Streptococcic Disease		Nonstreptococcic Disease	
	Number	Per Cent	Number	Per Cent
17 to 20	143	35.0	259	30.7
21 to 24	147	36.0	247	29.6
25 to 30	72	17.6	199	23.6
31 to 35	35	8.6	102	12.1
36 to 40	11	2.7	34	4.0
Over 40	1	0.2	4	0.5

Age.—Inadequate data were available which could be used for the purpose of comparing the actual attack rate in relation to age, since the composition of the study group in this respect was unknown. In table 3 the incidence of streptococcic and nonstreptococcic disease according to age of the affected persons is presented. Most of the infections in both groups were in men less than 30 years old, an incidence which was to have been expected since nearly all enlisted military personnel are in this age group.

Seventy-one per cent of the patients with hemolytic streptococcus infection, but only 60.3 per cent of those with infections not caused by this organism, were less than 24 years of age. Because the number of persons in the study is large, this small difference may be statistically significant.

Premilitary Residence.—The relative frequency of occurrence of streptococcic and nonstreptococcic disease has been compared with the premilitary residence of the infected persons. and no difference in suscep-

tibility to these infections was discovered. The data are presented in table 4.

Rheumatic Fever.—Many cases of rheumatic fever occurred among the personnel of the study post but were insufficient for epidemiologic consideration. Observations reported elsewhere [2] demonstrated that this disorder was invariably a sequel to infection by group A hemolytic streptococci.

TABLE 4.—*Relation of the Premilitary Residence to the Incidence of Streptococcic and Nonstreptococcic Disease of the Respiratory Tract*

Service Command	Approximate Area	Streptococcic Disease		Nonstreptococcic Disease	
		Number	Per Cent	Number	Per Cent
1	New England	42	10.0	75	8 9
2	New York, New Jersey	63	15 2	124	14 6
3	Pennsylvania, Maryland, Virginia	39	9 4	65	7 7
4	South Eastern	49	11 8	114	13 3
5	Southern Great Lakes	45	10 9	135	16 0
6	Western Great Lakes	41	9 9	72	8 5
7	North Central	49	11 8	98	11 6
8	South Central	48	11 6	91	10 8
9	Western	38	9 2	69	8 2

COMMENT

Before the recent war, relatively few studies had been made which permitted a comparison of the epidemiology of hemolytic streptococcic and "virus," or undifferentiated, diseases of the respiratory tract in closed groups containing a homogeneous population. Many reports [3] are available describing outbreaks of hemolytic streptococcus infection, particularly in relation to rheumatic fever.

Dudley [4] has outlined certain basic principles involved in the spread of disease of the respiratory tract in closed groups, which have recently been restated by Coburn [5] with special reference to hemolytic streptococcus infection. The factors involved in the development of epidemics of infection by these organisms were: (1) the frequent introduction of highly susceptible persons into a population with a rapid turnover of personnel; (2) overcrowding, particularly in sleeping quarters;

2. Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, Arch Int Med. **76**:131 (Sept.) 1942.

3. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, Metropolitan Life Insurance Co. for the American Heart Association, New York, 1943.

4 Dudley, S. F.: The Spread of Droplet Infection in Semi-Isolated Communities, Medical Research Council, Special Report Series, no. 3, London, His Majesty's Stationery Office, 1926.

5 Coburn, A. F., in The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, Washington, D. C., Bureau of Medicine and Surgery, Navy Department, 1944.

(3) the presence among members of the community of pathogens commonly found in the respiratory tract of an extreme degree of communicability, and (4) outbreaks of measles or influenza which predisposed to infection by streptococci.

Wheeler and Jones[6] have failed to demonstrate that influenza was followed by an increase in the frequency of hemolytic streptococcus disease. A longer period of exposure was required to institute an outbreak of streptococcic infection than to institute one of "virus" infection when new recruits were introduced into a military establishment in which both types of disease were occurring frequently. These authors felt that a constant influx of such susceptible persons was most important for the maintenance of the epidemic state.

Other American investigators[7] have noted that the rapid spread of streptococci occurs more readily in the winter than in the fall. Civilian experience is similar in this country.[3]

This summary provides a suitable background for the consideration of the observations described in this report. The military population from which the study group of infected persons was derived was unstable but of a different nature from those described by others, who have usually considered the problems presented by disease of the respiratory tract in induction stations to which large numbers of recruits highly susceptible to infection are admitted for relatively short courses of training. These troops were nearly all well seasoned men who moved in and out of the post in large groups and who remained for long periods.

The epidemic dynamics of disease of the respiratory tract over an eighteen week period have been described. During the first eight weeks an outbreak of influenza A and another of undifferentiated disease of the respiratory tract, probably not this disease, occurred, neither of which was associated with or followed by an increase in the frequency of streptococcic infection.

The presence in the population of a large number of men who had been stationed in the post selected for study for several months was able to prevent the spread of streptococci, even though "virus" infection was prevalent and the season of the year appropriate. Later, the movement into the post of large groups of men of extended military experience was followed, on two occasions, by an increase in the incidence of undifferentiated disease of the respiratory tract and,

6. Wheeler, S. M., and Jones, T. D.: Factors in the Control of the Spread of Acute Respiratory Infections with Reference to Streptococcal Illness and Acute Rheumatic Fever, Am. J. M. Sc. **209**:58 1945.

7. Hodes, H. L.; Schwenkter, F. F.; Chenoweth, B. M., and Peck, J. L.: Scarlet Fever as an Airborne Infection, Am. J. M. Sc. **209**:64, 1945.

somewhat later, of streptococcic disease. More than 60 per cent of these illnesses occurred among men who had been stationed in the post for less than two months.

Outbreaks of virus infection may, therefore, be expected to occur among well seasoned troops, but it is probable that a definite increase in the frequency of streptococcic infection will be most likely to occur when such men are moved from an area in which disease caused by these organisms is uncommon to one in which it is well established.

Throughout the study period a few serologic types of hemolytic streptococci caused most of the infections. Following the introduction of new troops into the post in the eleventh week, there was an increase in the rate of streptococcic disease, and a few types which had not previously been isolated appeared but were not responsible for many cases. Most of the incoming men appeared to have been infected as the result of exposure to organisms present in the environment on their arrival and not of the enhancement of invasiveness by the new conditions of streptococci already present among them. No tendency toward the establishment of a monotype epidemic was demonstrated.

Since hemolytic streptococci and filtrable viruses are different physically and in many other respects, it was thought that a comparison of the incidence of the diseases caused by these organisms might indicate a difference in the type of host most suitable for each. A comparison of the infected persons on the basis of age, duration of service in the army and length of time in the post studied did not reveal convincing differences, except for the fact that men who had been in the camp for a brief period were more likely to be infected by streptococci.

Because streptococcic disease is believed[8] to be infrequent in the southern United States, it was thought that men whose premilitary residence had been in this area might be more susceptible to infection by these organisms, but they were not.

It may be stated in conclusion that men who had been stationed for a considerable period in the post studied were relatively resistant to infection by streptococci and that the spread of these organisms was not enhanced by preceding virus infection. Fresh seasoned troops were highly susceptible to infection by both agents, and there were no convincing differences in the type of men attacked by either, so far as they have been compared in this study.

SUMMARY

1. Certain aspects of the epidemiology of group A hemolytic streptococcus and nonstreptococcus disease have been studied.

8. Van Ravenswaay, A. C.: The Geographic Distribution of Hemolytic Streptococci: Relationship to the Incidence of Rheumatic Fever, J. A. M. A. **126**:486 (Oct. 21) 1944.

2. Prolonged residence in the post selected for study conferred a considerable resistance to streptococcic infection.

3. Infection by undetermined viruses common to the respiratory tract or by influenza A did not enhance the spread of streptococci.

4. The introduction of well seasoned troops from another area was followed by an increase in the incidence of both streptococcic and nonstreptococcic disease of the respiratory tract.

5. Infection by viruses and by streptococci occurred among men who were similar when compared as to age, duration of military service and premilitary residence.

PROGRESSIVE BILATERAL BULLOUS EMPHYSEMA

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APART from emphysema of the bullous type, which is not unusual and occurs in all parts of the lung, there appears to be a different, more uncommon form. Its characteristics are striking enough for one to regard it as an entity, for which we propose the name "progressive bilateral bullous emphysema." The disease is usually recognized after the second decade and is apparently limited to men. The process begins in the apexes and gradually increases, until in extreme cases both upper and lower lobes are replaced by large cystlike areas. The usual history is that of cough, slowly increasing dyspnea, recurrent infections of the respiratory tract, asthma-like attacks and cachexia. Death occurs from intercurrent infections or when insufficient pulmonary tissue is left to carry on normal respiratory exchange.

The following 8 cases were observed in the Jefferson Hospital during a period of three years.

CASE 1.—A 48 year old white painter was admitted to the ward on Oct. 12, 1942, with progressive dyspnea, increasing weakness, chronic cough and susceptibility to colds. There was a 14 pound (6.4 Kg.) loss of weight during the year.

The patient was dyspneic, even at rest. The chest was emphysematous and was hyperresonant to percussion, with distant breath sounds over the upper lobes. The hemoglobin level was 98 per cent, and the erythrocyte count was 4,500,000. The vital capacity was 1,700 cc. A roentgenogram of the chest (fig. 1) on Nov. 11, 1942 showed replacement of the upper lobes with numerous bullae, which compressed the lower lobes. Only a small amount of respiratory tissue remained at the bases. The pulmonary conus was more prominent than normal.

After the aspiration of air from the bullous portion of the left lung, the dyspnea was temporarily relieved. The patient was discharged unimproved on Dec. 24, 1942.

CASE 2.—A 51 year old man entered another hospital in June 1940, with the complaint of increasing shortness of breath and moderate cough with some mucopurulent expectoration. He dated the onset of his symptoms to an attack of pleurisy which had occurred two years before. A roentgenogram taken in June 1940 (fig. 2A) revealed bullous emphysema of the upper half of both pulmonary fields, more pronounced on the right. Interstitial fibrosis was seen in the hili and the lower pulmonary fields. The heart was normal in appearance. During the next four months he lost 25 pounds (11.3 Kg.) and became weaker.

Examination on his admission to the Jefferson Hospital, Oct. 16, 1940, showed emphysema with distant breath sounds over the upper lobes of both lungs. The
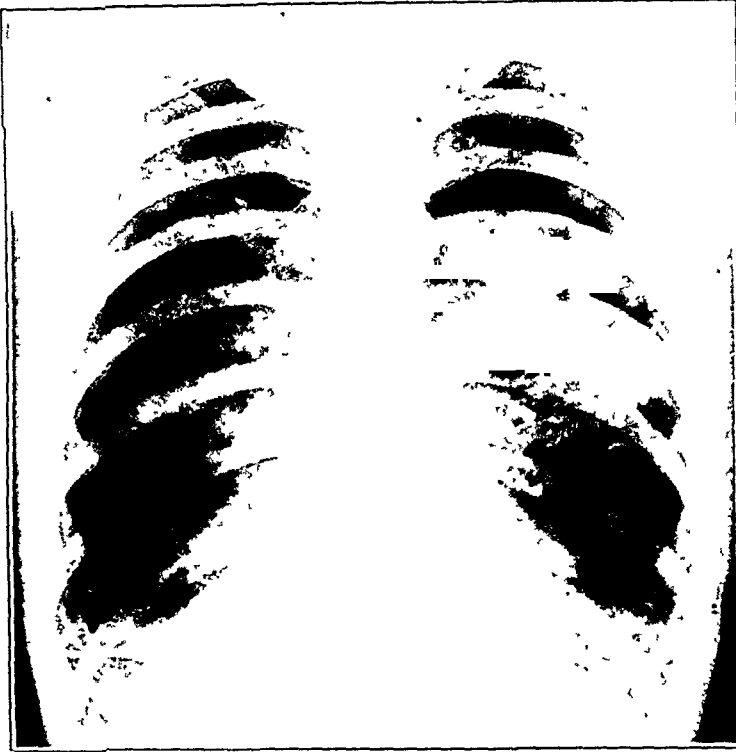
Fig. 1. (case 1).—Prominent pulmonary conus and replacement of upper lobes with numerous bullae, which compress the lower lobes of the lungs.

Fig. 2 (case 2).—*A*, roentgenogram taken June 26, 1940. *B*, four months later there are slight increase in the bullous emphysema and development of prominent pulmonary conus.

hemoglobin level was 97 per cent with 4,900,000 erythrocytes. A bronchoscopic examination showed evidence of chronic tracheobronchitis and mucopurulent secretion. A roentgenogram (fig. 2 B) showed a slight increase of the bullous emphysema over that shown in the previous film. The pulmonary conus had now become prominent. The patient was symptomatically improved after the bronchoscopic aspiration of 40 cc. of mucopus and was discharged on October 22.

Subsequently all the respiratory symptoms increased in severity, and later roentgenograms (fig. 3) taken at another hospital showed an increase in the bullous emphysema with pneumonitis at the base of the upper lobe of the left lung. The pulmonary conus was even more prominent. The patient died of respiratory failure on March 18, 1942.

Postmortem examination showed a poorly nourished middle-aged white man. The finger nails were curved. The chest was long, and the ribs were curved outward, producing a barrel-shaped chest. The diaphragm was depressed to the level

Fig. 3 (case 2).—*A,* five months after figure 2 *B,* there is increase in emphysema with pneumonitis at the base of the upper lobe of the left lung and greater prominence of the pulmonary conus. *B,* lateral view.

of the seventh rib on both sides. The right pleural cavity contained about 500 cc. of fluid. There were numerous dense fibrous adhesions binding both lungs to the parietal pleura, mediastinum and pericardium. Both lungs, especially the right, contained numerous air-filled emphysematous sacs, which overlay the pericardium. The sacs varied from 2 mm. to 12 cm. in diameter. Two larger bullae almost replaced the upper lobe of the right lung. They consisted of an extremely thin transparent wall and contained air under pressure. The lining tissue was smooth, although in some cases there were numerous thin bands or ridges on the inner surface. The bronchi were uniformly dilated. The mucosa was thickened and dark brown and was covered by a tenacious, thick grayish brown exudate. Careful examination of the bronchi failed to reveal any point of obstruction. The lower lobe of the right lung contained no bullae and was collapsed by the effusion. The pulmonary tissue

elsewhere was soft and grayish pink. The heart weighed 380 Gm. The enlargement was due to hypertrophy and dilatation of the right ventricle and moderate dilatation of the right auricle. The endocardium was smooth. There were a few atheromatous deposits in the substance of the mitral valve. The coronary arteries were patent. There were moderate atherosclerosis of the ascending aorta and a few small plaques on the larger branches of the pulmonary artery. The stomach and remaining portions of the gastrointestinal tract were not unusual. The liver weighed 1,300 Gm. and was not enlarged but had been displaced downward on the right side. A large portion of the capsule on the anterior surface was thickened, smooth and yellowish gray. The cut surface revealed moderate congestion. The gallbladder, bile ducts, pancreas, spleen, adrenal glands, bladder and prostate appeared normal. The kidneys were normal in size, weighing 140 and 150 Gm. On the surface of each kidney were two or three thin-walled cysts 5 to 15 mm. in diameter, filled with clear amber

Fig. 4 (case 3).—Extensive bullous emphysema of the upper lobes of both lungs, effusion at the base of the right lung and prominent pulmonary conus.

fluid. The lining was thin and smooth. The cortexes and medullas were otherwise normal.

The anatomic diagnoses were bilateral bullous emphysema of the upper lobes, chronic bilateral fibrous pleuritis, pleural effusion on the right side, hypertrophy and dilatation of the right ventricle, chronic capsulitis of the liver and multiple cortical cysts of the kidneys.

CASE 3.—A 57 year old white merchant was admitted to the hospital on Dec. 26, 1939. He complained of cough and precordial pain of five days' duration and edema of the ankles of two weeks' duration. For two years he had progressive dypsnea and weakness.

Examination showed emphysema of the chest, distant breath sounds over the upper lobes and fine rales at the bases. The heart was enlarged to percussion, and

pretibial edema was present. The blood pressure was 120 systolic and 80 diastolic. Electrocardiographic changes were interpreted as severe myocardial degeneration and right axis deviation. The hemoglobin content was 94 per cent and the erythrocyte count 4,600,000.

A roentgenogram of the chest (fig. 4) showed extensive bullous emphysema of the upper lobes of both lungs. The remaining pulmonary fields were congested, with interstitial fibrosis in the lower lobes. There was an effusion at the base of the right lung. The heart was enlarged, with a prominent pulmonary conus.

Improving with symptomatic treatment, the patient was discharged Jan. 1, 1940.

CASE 4.—A 36 year old white man, a welder, was admitted to the hospital on April 18, 1943. His chief complaint was a chronic cough for fifteen years, asthmatic-like attacks during the past five years and gradually increasing dyspnea. Examination showed an emphysematous chest with occasional rales at the bases.. The hemoglobin level was 84 per cent and the erythrocyte count 4,800,000.

Fig. 5 (case 4).—A, emphysema of the upper lobes of both lungs; B. a bronchogram demonstrating depression of the bronchial tree and a corrugated appearance of the bronchial tree suggesting early bronchiectasis.

A roentgenogram in 1941 showed advanced bullous emphysema of the upper lobes of both lungs. There was interstitial fibrosis in the lower lobes and hili. The heart had a prominent pulmonary conus but was not enlarged.

The roentgenogram on April 19, 1943 (fig. 5 A) showed some increase in the bullous emphysema but no other changes. Bronchoscopic examination revealed chronic inflammatory changes with mucosal thickening in all the main bronchi. A bronchogram (fig. 5 B) demonstrated a depression of the bronchial tree by the emphysematous upper lobes. A peculiar corrugated appearance in the entire bronchial tree suggested early bronchiectasis. The patient was discharged May 8, 1943, unimproved.

CASE 5.—A white man aged 49 was admitted to the hospital on Aug. 3, 1943. He complained of cough for twelve weeks with expectoration of mucopurulent

sputum. The cough had become severer. For the past seven years he had had increasing dyspnea, which at the time of his admission occurred with the least exertion. There was vague discomfort in the chest.
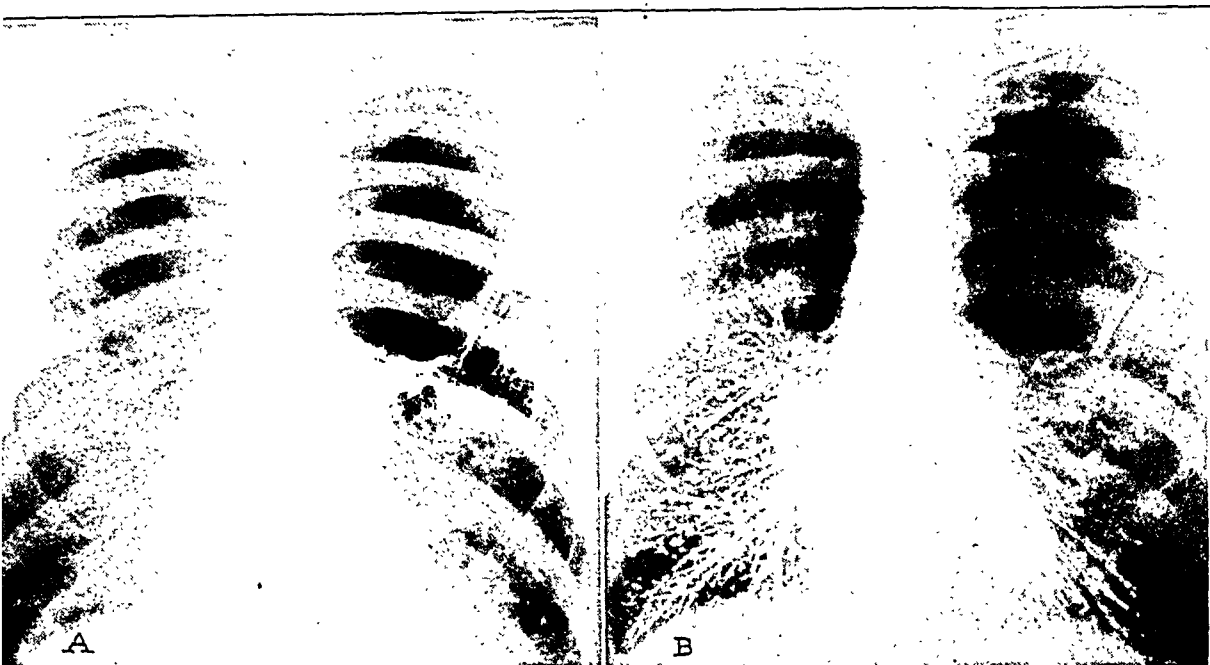

Fig. 6 (case 5).—Extensive bullous emphysema of the upper lobes and bronchogram illustrating depression of the bronchial tree.
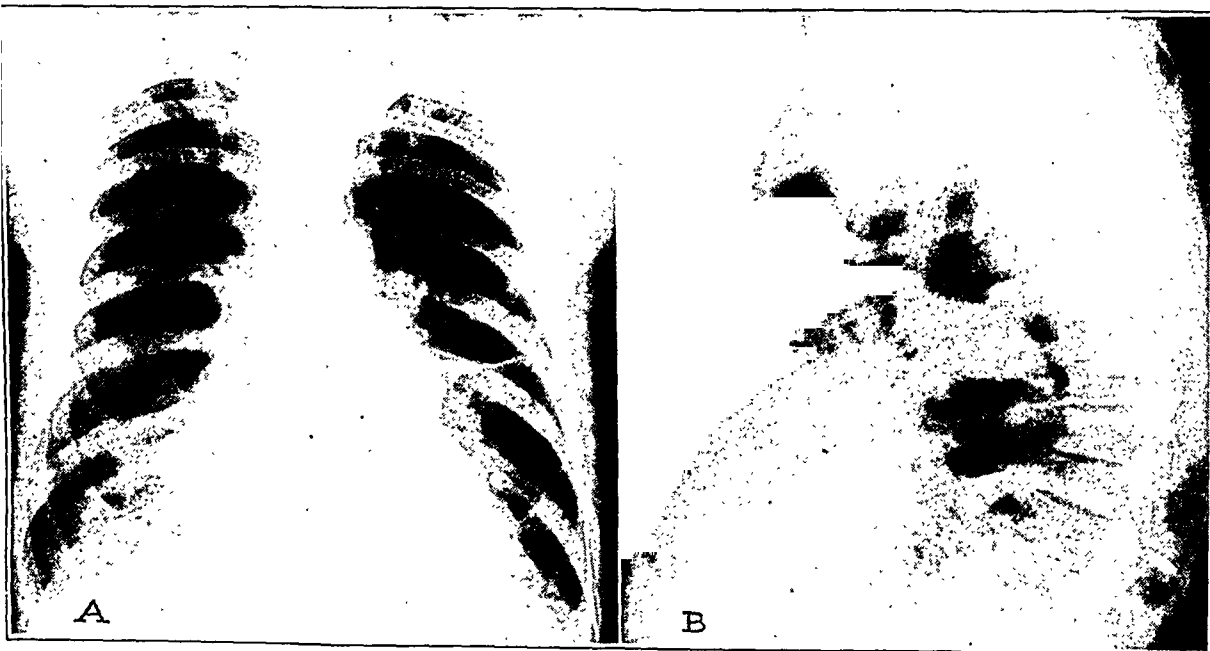

Fig. 7 (case 6).—Moderately enlarged heart with prominent pulmonary conus. *A,* front view and *B,* lateral view.

Examination revealed emphysema with distant breath sounds, especially over the upper lobes. The vital capacity was 2,300 cc. The hemoglobin content was 95 per cent, and the erythrocyte count was 4,800,000. A roentgenogram made two

years before his admission to the hospital showed extensive bullous emphysema of the upper lobes of both lungs with interstitial fibrosis in the lower pulmonary fields. The pulmonary conus was prominent, but the heart was not enlarged. A roentgenogram (fig. 6 *A*) on July 7 showed no extension of the bullous involvement. A bronchogram (fig. 6 *B*) showed depression of the bronchial tree by bullae of the upper lobes. There was no bronchiectasis. The patient was discharged unimproved on August 31.

CASE 6.—A 62 year old white watchman was admitted to the hospital on Aug. 28, 1943. His chief complaint was gradually increasing dyspnea for thirty years and a mild cough for ten years with expectoration. In the past few weeks mild edema had developed at his ankles.
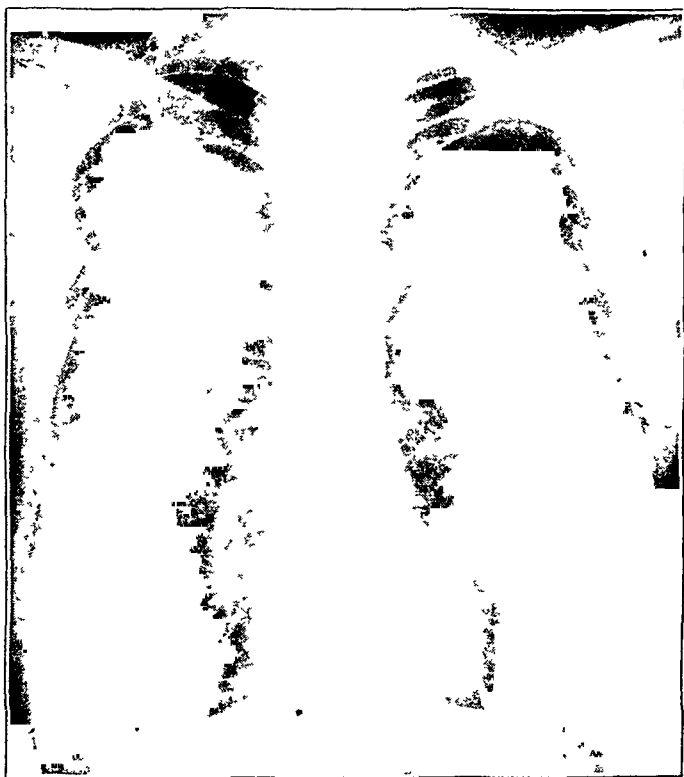

Fig. 8 (case 8).—Generalized emphysema with giant bullae in the upper lobes.

Examination showed an emphysematous hyperresonant chest, and occasional rales were present in the bases. The heart was enlarged to percussion, and the heart sounds were distant. The vital capacity was 700 cc. The electrocardiogram revealed myocardial degeneration and right axis deviation. The hemoglobin content was 90 per cent and the erythrocyte count was 4,500,000. Roentgenograms of the chest (fig. 7) on Aug. 30, 1943 showed a moderately enlarged heart with a prominent pulmonary conus. Multiple small emphysematous bullae filled the upper pulmonary fields. There was interstitial fibrosis in the lower pulmonary fields. The patient was discharged unimproved.

CASE 7.—A 50 year old white man, a shipper, entered the outpatient department with a complaint of progressive dyspnea for five years. A slight cough had also been present, and he had lost 40 pounds (18.1 Kg.), in the past two years.

Examination revealed slight pulmonary emphysema. The hemoglobin content was 91 per cent. A roentgenogram on Sept. 10, 1943 showed general emphysema with bullous formation in the upper third of the pulmonary fields, more striking on the right. The pulmonary conus was prominent, but the heart was not enlarged. Further studies could not be made.

CASE 8.—A 53 year old white man, a tool grinder, entered the outpatient department, complaining of increasing cough and expectoration for five years. For the past six months he had been getting increasingly dyspneic. He had lost 10 pounds (4.5 Kg.) in the year. Examination showed nothing more than an emphysematous chest. The vital capacity was 2,700 cc. A roentgenogram (fig. 8) showed generalized emphysema with giant bullae in the upper lobes, especially on the left. The heart was not unusual.

COMMENT

The number of features common to these reported cases and to those reported elsewhere favors the view that the disease is an entity. The roentgenographic changes in the lungs are similar in all. In the upper pulmonary fields the walls of the bullae replace the normal markings by a patternless tracery of fine linear shadows. Confluence of some bullae and discreteness of others cause great irregularity of size and shape. In some instances they are high and cystlike, replacing the upper lobe (figs. 1, 2, 5 and 6); in others they are numerous and small (figs. 4 and 7), and in far advanced cases the lower lobes are compressed (fig. 1). The lower pulmonary fields usually show the markings of increased density of interstitial fibrosis. The thorax appears lengthened because of the depressed diaphragm, which draws the mediastinal tissues with it. Bronchography with iodized oil for 2 patients (cases 4 and 5, figs. 5 and 6) showed great depression of the bronchi of the upper lobes by the bullae. The peculiar corrugation of the bronchus in case 4 (fig. 5) suggests the early changes of bronchiectasis. In nearly all cases the pulmonary conus of the heart is enlarged, sometimes with considerable rapidity (case 2, figs. 2 and 3) as a result of an overload on the right side of the heart caused by compression and destruction of much pulmonary tissue.

In the 8 cases of this series and the 13 cases reported elsewhere [1] (table) all the patients were men. The symptoms usually began

1. (*a*) Burke, R. M.: Vanishing Lungs: Case Report of Bullous Emphysema, Radiology **28**:367-371 (March) 1937. (*b*) Jaubert de Beaujeu, A.; Abdallah, T. B., and Picard, P.: Emphysème pulmonaire, symétrique à bulles géantes multiples, Presse méd. **48**:283-284 (March 12) 1940. (*c*) Lewis, J.: Chronic Bilateral Spontaneous Pneumothorax, Brit. M. J. **2**:779-780 (Oct. 28) 1933. (*d*) Korol, E., and Ensign, C. F.: Bullous Emphysema? Or Bilateral Pneumothorax? Radiology **23**:223-227 (Aug.) 1934. (*e*) Long, E. R.: Multiple Giant Pneumatoceles of Lung (Giant Bullae of Lung, Bullous Emphysema, Cystic Bronchiolectasis, Polycystic Lung, etc.), Internat. Clin. **3**:1-5 (Sept.) 1940. (*f*) Harris, H. J.: Extensive Destruction of Lungs; Emphysema with Giant Bullae; Autopsy, Radiology **36**:492-

to be obvious in the third and fourth decades; in 1 patient, aged 57, (case 3) symptoms began at 55. In all instances there were cough with some expectoration and increasing dyspnea, and in many, asthma-like attacks, weakness and loss of weight. The prognosis is poor, with slow progression over years and with persistent or recurrent attacks of the symptoms just mentioned. Thus far, the longest periods of observation have been seven years [1g] and eight years.[1f] No case has as yet been reported in which the disease was in the presymptomatic

Summary Data of Cases of Progressive Bilateral Bullous Emphysema

Reported by	Age	Age at Onset	Symptoms			Typical Roentgenologic Findings	Outcome
			Dyspnea	Cough	Asthma		
Lewis [1c] (1933)	49	42	+	..	+	Yes	?
Korol [1d] (1934)	35	25	+	..	..	Yes	?
	37	27	+	+	..	Yes	Slow progression 10 years
Burke [1a] (1937)	28	28	+	+	..	Yes	Progression with death at age 35; autopsy
Kaltreider and Fray [1h] (1939)	35	28	+	+	..	Yes	Died; autopsy revealed anthracosilicosis, fibrosis and bullae
Wiese, Heiken, Charr [1j] (1939)	39	35	+	+	..	Yes	Died; anthracosilicosis, fibrosis and bullae
Beaujeau [1b] (1940)	28	27	+	+	..	Yes	?
Long [1e] (1940)	40	?	..	..	..	None taken	Died; autopsy showed typical bullae
Raman [1g] (1941)	37	36	+	+	..	Yes	?
	40/50	?	+	+	..	Yes	?
	34	27	+	+	..	Yes	Died; no autopsy
Harris [1f] (1941)	41	33	+	+	..	Yes	Died; no autopsy
Allison [1i] (1942)	41	40	+	+	..	Yes	?
Present series:							
Case 1	48	47	+	+	..	Yes	
Case 2	51	49	+	+	..	Yes	
Case 3	57	55	+	..	..	Yes	
Case 4	36	31	+	+	+	Yes	
Case 5	49	37	+	+	..	Yes	Died; autopsy
Case 6	62	32	+	+	..	Yes	
Case 7	50	45	+	+	..	Yes	
Case 8	53	48	+	+	..	Yes	

stage, although one can safely predict that such would be found if mass roentgenography of all patients admitted to hospitals were employed. The progressive nature of this type of emphysema is evident from reported cases, which showed slow progression over a period of

494 (April) 1941. (*g*) Raman, T. K.: Bullous Emphysema of Lung, Indian M. Gaz. **76**:515-516 (Sept.) 1941. (*h*) Kaltreider, N. L., and Fray, W. W.: Pathological Physiology of Pulmonary Cysts and Emphysematous Bullae, Am. J. M. Sc. **197**:62-77 (Jan.) 1939. (*i*) Allison, S. T.: Vanishing Lung: Report of Case of Advanced Bullous Emphysema, Ann. Int. Med. **17**:139-148 (July) 1942. (*j*) Wiese, E. R.; Heiken, C. A., and Charr, R.: Multiple Giant Bullae Associated with Anthracosilicosis, Am. J. Roentgenol. **42**:186-191 (Aug.) 1939.

years.[2] In the case reported by Lewis [1c] there were small translucencies at the apexes with absence of pulmonary markings. This was interpreted as bilateral apical pneumothorax. We have seen 2 similar cases. This may be the earliest manifestation of progressive bullous emphysema. The bullae, apparently, begin in the apexes and gradually extend downward.

Of the 6 fatal cases, reported by others, in all of which the patients were under 42, death apparently resulted from the advancing disease itself. One of our patients died at 51 (table). There was no case studied at necropsy which disclosed a clue to the primary cause of the disease. In 2 cases,[1h] there were anthracosilicosis and perihilar fibrosis. In 1,[1e] simple giant bullae were found and in another [1f] purulent bronchitis and indurated peribronchial tissues, all probably incidental or resultant changes.

The unique appearance of the roentgenogram makes diagnosis relatively simple. The only disease important in differential diagnosis is cystic disease of the lung, in which clearcut rounded cysts are discernible and present anywhere in the lung, not exclusively in the upper lobes.

There is no effective treatment. Prophylactically it would seem desirable to reduce incidental infections of the respiratory tract to a minimum, to prohibit smoking and strenuous labor, to advise living in an equable climate and to observe hygienic measures conducive to good health.

The cause of the condition is unknown. Allison [11] suggested "chronic respiratory strain" resulting from chronic bronchitis and asthma as a factor, but he grouped the disease with ordinary chronic obstructive emphysema. Christi [3] made the following classification of types of emphysema: (1) chronic obstructive or hypertrophic emphysema, in which group Allison [11] has stated that he feels "vanishing lung" belongs; (2) senile or atrophic emphysema; (3) acute vesicular emphysema of the type seen in mountain climbers, which is usually reversible, and (4) localized or compensatory emphysema, most commonly seen in the uninvolved pulmonary fields in patients with pneumonia.

Although long-enduring "respiratory strain" was evident in our patients (cases 4 and 6), it is impossible to tell whether or not the symptoms indicated the cause or were the effect of the form of bullous emphysema present. Furthermore, the existence of either asthma or chronic bronchitis does not explain why men alone were affected or why the disease began bilaterally and in both apexes. The disease may be

2. Raman.[1g] Korol and Ensign.[1d] Wiese, Heiken and Charr.[1j]

3. Christie, R. V.: Emphysema of the Lungs, in. Rolleston, H.: British Encyclopedia of Medical Practice, London, Butterworth & Co., Ltd., 1937, vol. 4, pp. 508-519.

a form of chronic obstructive emphysema, but why the bullae should appear where and how they do is a mystery.

The apparent inconsistency that only 13 cases have thus far been reported as such in the literature and 8 cases were observed by us in a short period of three years may be explained partly by the possibility that similar cases may have been reported under a variety of names, such as bullous emphysema, giant bullous emphysema, giant symmetric bullous emphysema, cystic disease of the lungs, multiple cysts of the lung, cystic degeneration of the lungs, vanishing lung and others. The condition is probably far more common than the reported cases indicate, especially in the asymptomatic stage. Personal commentaries from a number of roentgenologists support this view.

SUMMARY

Eight cases of progressive bilateral bullous emphysema are presented, together with a review of 13 cases from the recent literature.

This type of emphysema appears to represent a fairly definite entity, beginning in both apical regions, progressively extending downward and occurring only in males.

Little is known of the cause, pathogenesis or treatment.

It is our opinion that this condition is more prevalent than the literature suggests.

FULMINATING MENINGOCOCCEMIA WITH VASCULAR COLLAPSE (WATERHOUSE-FRIDERICHSEN SYNDROME)

Report on Four Adult Patients Who Recovered

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NUMEROUS reports during the past two years indicated that the dramatic syndrome of fulminating meningococcic septicemia complicated by severe vascular collapse and widespread purpuric lesions involving the skin and almost any organ, including the adrenal glands, is being more frequently recognized ante mortem. Thomas and Leiphart,[1] in a publication appearing in July 1944, stated: "At the present time almost 150·cases have been reported, the vast majority in infants and young children. A careful search of the literature has revealed only 19 instances in adults." They reported 2 additional fatal cases in which the patients were adults. Prior to the advent of sulfon-·amide compounds the syndrome was considered universally fatal. In a report appearing in January 1945, Weinberg and McGavack[2] stated that recovery had been reported in only 11 cases of the Waterhouse-Friderichsen syndrome, and they added 1 case in which the patient recovered. A meningococcus was grown on culture of the blood from 6 of the 12 patients, a pneumococcus from 1 and Staphylococcus aureus from 1. For the 4 remaining patients the culture of the blood either showed no growth or was not recorded, but in 2 there were organisms in the spinal fluid.

The purpose of this paper is to report 4 nonfatal cases of fulminating meningococcemia occurring in adults, in which there were organisms grown on culture of the blood and profound vascular collapse—cases clinically indistinguishable from those of the Waterhouse-Friderichsen syndrome. All 4 patients were critically ill, and the prognosis was doubtful for each for a few hours. In addition, we wish to point out: (1) the changing trend of thought concerning pathogenesis, (2) the necessity for early clinical diagnosis and the futility of waiting for

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1. Thomas, H. B., and Leiphart, C. D.: Septicemia and Purpura with Adrenal Hemorrhage in the Adult, J. A. M. A. **125**:884 (July 29) 1944.

2. Weinberg. L. D., and McGavack, T. H.: The Waterhouse-Friderichsen Syndrome, New England J. Med. **232**:95 (Jan. 25) 1945.

laboratory aid and (3) the importance of energetic treatment to combat profound shock in this syndrome.

By definition and by popular conception the Waterhouse-Friderichsen syndrome has been considered as a fulminating septicemia which is marked by sudden onset, with hemorrhage in the skin and mucous membranes plus bilateral destruction of the adrenal glands by extensive hemorrhages, resulting in vascular collapse and death. This time-honored conception should be reevaluated, since Williams [3] observed 17 cases of fatal fulminating meningococcic septicemia occurring in children, all with similar clinical observations but in which necropsy revealed bilateral adrenal hemorrhages in only 9. This report forces one to accept one of the following postulates: (1) that the profound vascular collapse or shock is produced by an overwhelming septicemia and that the adrenal hemorrhages are coincidental with hemorrhages elsewhere or (2) that in some cases the vascular collapse is due to the overwhelming septicemia while in others it is due to the combination of septicemia and adrenal hemorrhages. Regardless of which postulate one accepts, septicemia with vascular collapse remains the primary factor, and bilateral adrenal hemorrhage may or may not be added. The former postulate seems more tenable for reasons to be pointed out later, in the comment on pathogenesis.

Based on this reasoning, the attempt to make an early clinical diagnosis without laboratory aid and to start immediate energetic treatment of the profound vascular collapse in conjunction with intravenous administration of sodium sulfadiazine for the septicemia seemed justifiable. Four patients have been seen, who represent 2.6 per cent of all persons with meningococcic infections admitted to this hospital. This figure approximates the 3.3 per cent of 485 cases reported from army camps and cited by Weinberg and McGavack.[2]

PATHOGENESIS

The theory of hemorrhagic destruction of the adrenals, long accepted as the cause of death in this dramatic illness, becomes questionable for several reasons:

1. Thomas and Leiphart [1] pointed out that the explosive development of the Waterhouse-Friderichsen syndrome, which requires but a few hours, is in decided contrast to the slow development of symptoms over a period of a few days in completely adrenalectomized animals. 2. The previously mentioned report of Williams [3] proved that hemorrhagic destruction of the adrenal glands is not the only cause of death, since bilateral adrenal hemorrhage was not revealed at necropsy in

3. Williams, H.: Meningococcal Infections in Infancy and Children, M. J. Australia **2**:557, 1942.

8 of his 17 cases.   3. The therapy with cortical substance in the cases herein reported would not have prevented recurrence of symptoms of adrenal insufficiency if hemorrhagic destruction of the adrenal glands had occurred.   4. If destruction of the adrenal glands had caused the severe vascular collapse in our patients, regeneration could not have been sufficiently rapid to prevent recurrence of symptoms when cortical substance was given for such short periods.

In view of these facts, it is plausible to postulate that the overwhelming septicemia produces severe shock and that if this state remains untreated the shock becomes irreversible. adding to the capillary damage and hemorrhagic manifestations, which coincidentally involve the adrenal glands in some cases.

<div align="center">REPORTS OF CASES</div>

CASE 1.—A white man aged 32 gave a history of becoming acutely ill the night of Jan. 20, 1944, with chilliness, nausea, vomiting, headaches and increasing weakness.   He noted a petechial rash the morning of January 21 and was admitted to the hospital at 2:30 p. m.

On admission to the ward he appeared seriously ill.   His skin was ashen gray and his lips, fingers and toes cyanotic.   His extremities were cold, and he was perspiring profusely.   The temperature was 103.6 F.; the systolic blood pressure was 100 mm. of mercury and the diastolic 60.   Over the thorax, back and forearms large petechiae were noted.   The white blood cells numbered 7,150, with 84 per cent neutrophils.   The spinal fluid contained 244 white blood cells, 93 per cent of which were neutrophils.   Cultures of the blood and of materials from the throat were made.   (It was later reported that they were positive for Neisseria intracellularis, group V.)   An infusion of 1,000 cc. of 10 per cent dextrose solution was given.   Within an hour after the patient's admission, his pulse had little volume and the systolic blood pressure was 68; the diastolic pressure reading was unobtainable.   His neck was not rigid; he was sweating profusely and was restless, sighing and tossing about the bed, and recovery seemed doubtful.   Five grams of sodium sulfadiazine, 500 cc. of plasma, 1,000 cc. of 10 per cent dextrose solution and 20,000 units of antimeningococcus serum were given intravenously in rapid succession, and 30 mg. of desoxycorticosterone acetate was given intramuscularly.   By 7 p. m. the blood pressure had risen to 100 systolic and 67 diastolic.   The pulse volume and the color had improved, but he was still perspiring freely.   The purpuric lesions were more extensive, and there was a slight puffiness about the eyelids.   He was quiet but apprehensive.   An infusion of 1,000 cc. of 10 per cent dextrose solution was given to replace the fluid lost by the profuse perspiration.   Between 7 and 11 p. m. there was improvement.   The sweating ceased, and his color approached normal.   During the night he received 2 Gm. of sodium sulfadiazine intravenously and 15 mg. of desoxycorticosterone acetate intramuscularly and a few hours later 3 Gm. more of sulfadiazine.   The systolic pressure varied from 112 to 94.   There was a moderate oliguria, with a total fluid intake of 4,180 cc. and an output of only 750 cc.

On January 22 he was much better during the morning; the blood pressure was 94 systolic and 68 diastolic.   His color was good; his temperature was 99.2 F. and his pulse 88.   Weakness remained, but he was comfortable.   Vomiting had ceased, and he was given 1 Gm. of sulfadiazine by mouth every four hours.   About

3 p. m. he became apprehensive and restless; the blood pressure dropped to 62 systolic and 40 diastolic. An infusion of 500 cc. of plasma was given. By 8 p. m. he was comfortable again, and the blood pressure was 114 systolic and 68 diastolic. During this twenty-four hour period he received 45 mg. of desoxycorticosterone acetate intramuscularly.

On January 23 he was comfortable and had improved. Systolic pressure varied from 90 to 114 and diastolic from 60 to 64. He received 30 mg. of desoxycorticosterone acetate, which was then discontinued.

On January 24 his condition was excellent; his blood pressure was 110 systolic and 50 diastolic. His later course and recovery were uneventful except for the occurrence of urticaria on January 31, probably due to the antimeningococcus serum.

CASE 2.—A white youth aged 18 gave a history of having experienced headache, fever and a sensation of chilliness for only a few hours before his admission to the hospital at 11 p. m., Jan. 25, 1944. When he arrived in the ward, he did not appear seriously ill. Later in the night he was reexamined; his temperature was 103 F., and a faint petechial rash was noticed. He was again reexamined at 8 a. m. on January 26. He appeared critically ill and drowsy but mentally clear. The petechial rash had increased; the lips, fingers and toes were cyanotic. The extremities were cold, and he was perspiring freely. The blood pressure was 74 systolic and 50 diastolic. The white blood cells numbered 15,210; the spinal fluid was normal. Blood was drawn for culture (later reported as positive for N. intracellularis, group I). Twenty-five milligrams of desoxycorticosterone acetate was given intramuscularly, and 5 Gm. of sulfadiazine was given intravenously, followed by 1,000 cc. of 5 per cent dextrose solution. There was slight objective improvement, and the systolic blood pressure was 82 by 12:45 p. m. Five hundred cubic centimeters of plasma was given intravenously at 1:30 p. m. At 2:45 p. m. the blood pressure was 104 systolic and 63 diastolic. His color had improved, and sweating had ceased. During the night of January 26 the temperature did not exceed 100 F.

By 8 a. m. January 27 he had received a total of 55 mg. of desoxycorticosterone acetate intramuscularly and 10 Gm. of sulfadiazine intravenously. He no longer appeared acutely ill. The temperature was 99 F. and the blood pressure 98 systolic and 50 diastolic. Nausea had ceased, and he was given 1 Gm. of sulfadiazine by mouth every four hours. He received 15 mg. desoxycorticosterone acetate.

On January 28, the temperature was 99 F. and the blood pressure 100 systolic and 50 diastolic. He was given an additional 15 mg. of desoxycorticosterone acetate, which was then discontinued.

The later course was uneventful, and he made a rapid recovery, except that sulfanilamide had to be substituted for sulfadiazine for a thirty-six hour period owing to the appearance of grossly bloody urine.

CASE 3.—A white man aged 28 became suddenly ill with nausea, vomiting, weakness and chilliness about 4:30 p. m. June 1, 1944. He was admitted to the hospital four hours later with a temperature of 103 F. He did not appear seriously ill when examined soon after his admission. The blood pressure was 86 systolic and 52 diastolic and the pulse rate 110. A few scattered petechiae were noted. At 4 a. m. his temperature reached the peak of 107 F. but dropped to 102 F. by 5 a. m.

On June 2 his temperature was 99 F., and the blood pressure was 85 systolic and 50 diastolic at 8 a. m. Petechiae had become more numerous and were present

in the conjunctivas. He was vomiting repeatedly and complained of abdominal pain. With dramatic suddeness, he became apprehensive, restless and progressively weaker. The blood pressure reading was not obtainable at 10.30 a. m. Petechiae were coalescing to form larger purpuric areas. He continued to be restless, perspired profusely and was pale but remained mentally clear. The neck was not rigid. Blood was drawn for culture (later reported positive for N. intracellularis, group II A). Five hundred cubic centimeters of plasma and 5 Gm. of sodium sulfadiazine were given intravenously. Desoxycorticosterone acetate was given hourly, usually in 5 mg. doses. The systolic blood pressure reading was 50 at 1 p. m. and unobtainable at 1:30 p. m. A third infusion of 500 cc. of plasma was given. The systolic blood pressure varied from 0 to 52; the pulse rate was not obtainable at times, and cyanosis was extreme. Twenty milligrams of desoxycorticosterone acetate and a fourth infusion of 500 cc. of plasma were given. At 4 p. m. there was a slight puffiness of the face and eyelids, but there was less cyanosis. The pulse was perceptible, and the blood pressure was 84 systolic and 44 diastolic. Throughout the night periodic vomiting continued, and the systolic pressure varied from 88 to 94. During the twenty-four hour period he received 9 Gm. of sodium sulfadiazine, 8 cc. of an extract of adrenal cortex (Eschatin) and 40 mg. of desoxycorticosterone acetate. The total urinary output was only 780 cc. in spite of an intake of 3,390 cc.

By June 3 he had improved greatly. Nausea had ceased, and he was able to take 1 Gm. of sulfadiazine every four hours by mouth. He complained of pain in the fingers and toes, but swelling and redness were not noticeable. The systolic pressure during the day varied from 90 to 100 and the diastolic from 50 to 70. His temperature did not exceed 100 F., and the pulse rate remained below 100. He received 5 cc. of extract of adrenal cortex and 15 mg. desoxycorticosterone acetate during the twenty-four hour period.

On June 4 he continued to improve subjectively and objectively. No essential change occurred in blood pressure and in temperature. He received 5 mg. of desoxycorticosterone acetate and 4 cc. of extract of adrenal cortex, which was then discontinued. On June 5 improvement was definite. Penicillin therapy was substituted for sulfadiazine owing to a rapidly developing anemia. By June 6 soreness in the fingers and toes had disappeared.

The remaining course was uneventful except for the treatment of the severe anemia and a prolonged convalescence.

CASE 4.—A white youth aged 18 was well on Jan. 20, 1945, but about 1 a. m. on January 21 he was awakened by a sensation of chilliness and nausea. He vomited twice, went back to bed and slept until 6 a. m. During the morning of January 21 he vomited several times; a diarrhea developed, and he felt intensely weak and chilly. He could not clearly recall events that occurred two or three hours prior to his admission to the hospital at 2:30 p. m.

On arriving in the ward he was in a state of shock, was critically ill, restless and apprehensive and was sweating profusely. The blood pressure was 68 systolic and 44 diastolic. The pulse rate was rapid and of poor volume and the temperature 100.8 F. An extensive purpuric rash was noted on the extremities and the trunk. There was no nuchal rigidity, and the lungs were resonant and clear. A clinical diagnosis of fulminating meningococcemia with vascular collapse was made, and treatment was started immediately without waiting for laboratory diagnosis. A continuous infusion of plasma, totaling 1,500 cc., was started. Culture of materials from the pharynx, of venous blood and of materials from petechiae were made (reported positive for N. intracellularis, group II A, at a later date). Five grams of sodium sulfadiazine was given intravenously and

10 mg. of desoxycorticosterone acetate intramuscularly. There was gradual subjective and objective improvement during the following two hours. The blood pressure rose slowly to 99 systolic and 40 diastolic. He became less apprehensive and stated that he felt better. At 6:30 p. m. he was cooperative, quiet, well oriented and less apprehensive. The blood pressure was 92 systolic and 50 diastolic and the temperature 102 F. His face and eyelids appeared·slightly puffy. At 10:30 p. m. he complained of feeling weak and continued to vomit periodically. The blood pressure was 88 systolic and 60 diastolic.

On January 22, about 1 a. m., the systolic pressure dropped to 74, and he was more réstless and apprehensive. An infusion of 500 cc. of plasma was started, making a total of 2,000 cc. given since admission. He voided a few ounces of dark amber urine, the first since his admission to the hospital. At 6:30 a. m. the blood pressure was 99 systolic and 60 diastolic, but he still complained of being weak. The systolic pressure remained about 90 and the diastolic 60 throughout the day, and there was little change in his condition. Nausea had ceased, and he was given 2 Gm. of sulfadiazine by mouth every four hours.

On January 23 the blood pressure throughout the day varied from 90 systolic and 60 diastolic to 95 systolic and 65 diastolic. The temperature remained approximately 101 F. He complained of pain in the ankles, knees and small joints of the hands and feet, and there was some swelling of the interphalangeal joints. Many of the petechiae had coalesced, forming larger purpuric spots.

On January 24 he was much improved. The dose of sulfadiazine was reduced to 1 Gm. every four hours by mouth. The systolic blood pressure varied from 95 to 100; the temperature was 101 F.

On January 25 the patient looked well. The pains in the joints had improved. The systolic blood pressure remained above 100.

The remaining convalescence was rapid and uneventful.

DIAGNOSIS AND TREATMENT

This syndrome should be included in the differential diagnosis when any patient appears ill to a degree out of proportion to the physical findings, especially if the illness is of less than thirty-six hours' duration. Undue collapse, weakness, restlessness, apprehensiveness, pallor, profuse sweating, vomiting, diarrhea, decreased or decreasing blood pressure and pulse of poor volume may occur in almost any combination and should cause the examiner to institute a diligent search for petechiae, which may be inconspicuous for a few hours. If petechiae are found, a tentative clinical diagnosis of Waterhouse-Friderichsen syndrome should be made and continuous infusion of plasma and adrenal cortex substitution therapy started. Blood should then be obtained for culture and complete blood count. Smears should be made from. petechial blood, which may reveal the organism in as high as 83 per cent of cases,[4] and the report of this examination should be available within one to two hours. The severity of the illness, however, dictates that one should give 5 Gm. of sodium sulfadiazine in 1,000 cc. of fluid intravenously

4. McLean, S., and Caffey, J.: Endemic Purpuric Meningococcus Bacteremia In Early Life, Am. J. Dis. Child. **42**:1053 (Nov.) 1931.

without waiting for laboratory aid, because petechial smears will not demonstrate the organisms in approximately one fifth of the cases. The futility of withholding chemotherapy for a report of culture of the blood is ridiculously obvious.

Although one is dealing with a fulminating infection, the absence of fever or the degree of fever at the moment of the examination should not be considered as evidence against meningococcemia. Case 3 emphasizes this point. The patient's recorded temperatures during the first twelve hours of hospitalization were 103, 107, 102 and 99 F.

The amount of sulfadiazine used in treatment of these 4 patients was not excessive. The plan of administration was to give an initial 5 Gm. of sodium sulfadiazine intravenously, followed by 2 or 3 Gm. intravenously every six hours until vomiting ceased and then 1 Gm. of sulfadiazine by mouth every four hours until the temperature had remained normal for three days.

The initial plasma infusion should be continued until there is a definite improvement in the blood pressure. The patient in case 4 received 1,500 cc. initially. In cases 2 and 3 a second drop in blood pressure, which was again controlled by the use of plasma, occurred the day after the patients' admissions. These 2 cases have prompted us to record the blood pressure every thirty to sixty minutes, depending on the severity of the illness at the moment, until the blood pressure has stabilized.

Early diagnosis is imperative if therapy is to be of any value, and in retrospect it appears that a clinical diagnosis could have been made and vascular collapse detected a few hours earlier in 3 of our cases. Therefore, we are routinely recording the blood pressure every thirty to sixty minutes in all proved or suspected cases of meningococcemia in which the patients appear acutely ill, hoping to detect any decided decrease of blood pressure and to institute supportive therapy before the vascular collapse reaches a critical level. Two additional patients have furnished presumptive evidence that this procedure is of value. They appeared seriously ill and had an extensive petechial rash. In both patients the blood pressures fell to 80 systolic and 40 diastolic; their pulse rates were 135 to 140, but their general appearance was not that of shock. An infusion of 500 cc. of plasma promptly restored their blood pressures to normal, and recoveries were uneventful. Adrenal cortex therapy was not employed. We believe these 2 patients might have had severe vascular collapse if plasma had not been given when the systolic blood pressure fell to 80. Fluids by the intravenous route, usually 5 per cent dextrose in an isotonic solution of sodium chloride, were given freely to keep the total intake above 3,500 cc. daily. According to the reports on recovered patients collected and tabulated

by Weinberg and McGavack,[2] the patients received liberal supportive treatment, chiefly in the form of intravenously administered dextrose and sodium hydrochloride solutions. The large fluid intake also helps prevent renal damage from the sodium sulfadiazine given intravenously.

Oxygen therapy is indicated during the first few hours when cyanosis is extreme.

We were not impressed by the beneficial effects, if any, of anti-meningococcus serum used in treatment of the patient in case 1 of this report or in the treatment of patients with other types of meningococcic infections.

Substitution therapy with varying amounts of adrenal cortex substance was attempted for a brief period. The patient in case 4 received only one dose of 10 mg. of desoxycorticosterone acetate. Eight of the 10 recovered patients who were reported on by Weinberg and McGavack [2] received adrenal cortex therapy; however, we are not aware of any valid proof of its value or any indication for its use in this syndrome except for the time-honored concept that vascular collapse is due to hemorrhagic destruction of the adrenals. At present, it probably should be used sparingly, and an effort should be made to determine its real value, if any.

<div align="center">SUMMARY.</div>

1. Four nonfatal cases of fulminating meningococcemia with severe vascular collapse occurring in adults, clinically indistinguishable from cases of the Waterhouse-Friderichsen syndrome, have been recorded. Treatment consisted of sulfadiazine, large amounts of plasma and fluids intravenously to combat the critical vascular collapse and adrenal cortex substance.

2. Deductive evidence suggests that hemorrhagic destruction of the adrenal glands is not the primary cause of death.

3. Early clinical diagnosis and prompt institution of therapy without waiting for laboratory aid are imperative.

ATYPICAL HEMOLYTIC ANEMIA

Observations with Particular Reference to the Use of Transfusions in the Study of Hemolytic Mechanisms

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TWO unusual cases of hemolytic anemia recently studied in the Strong Memorial Hospital presented excellent opportunities for exploring the usefulness of transfusion experiments in the investigation of hemolytic mechanisms.

As a matter of additional interest, the serum of the first patient contained autohemagglutinins active against human cells of all types at body temperature and α_1 agglutinins, active against A_1 cells only. The latter agglutinins have been described in detail in a separate paper [1] devoted to blood subgroups. Some of the features of the second case have also been presented in another publication,[2] which dealt with the in vivo maturation and destruction of the patient's reticulocytes after transfusion to a small child.

It has been amply demonstrated by means of the Ashby technic [3] and its various modifications [4] that transfused normal erythrocytes in the circulation of compatible "normal" recipients disappear in a linear fashion over a period of one hundred to one hundred and forty days.[5]

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1. Young, L. E.: Studies of the Subgroups of Blood Groups A and AB: I. Active and Passive Acquisition of Alpha₁ Agglutinins as a Result of Transfusion, J. Immunol. **51**:101-110 (Aug.) 1945.

2. Young, L. E., and Lawrence, J. S.: Maturation and Destruction of Transfused Human Reticulocytes, J. Clin. Investigation **24**:554-563 (July) 1945.

3. Ashby, W.: Determination of Length of Life of Transfused Blood Corpuscles in Man, J. Exper. Med. **29**:267-281 (March) 1919.

4. Dacie, J. V., and Mollison, P. L.: Survival of Normal Erythrocytes After Transfusion to Patients with Familial Haemolytic Anaemia, Lancet **1**:550-553 (May 1) 1943.

5. Wearn, J. T.; Warren, S., and Ames, O.: Length of Life of Transfused Erythrocytes, Arch. Int. Med. **29**:527-538 (April) 1922. Wiener, A. S.: Longevity

The cells are destroyed largely in accordance with their age, the oldest cells disappearing first. However, the recent studies of Dacie and Mollison[4] and Brown and associates[6] show that a much more rapid, exponential type of destruction of donated cells occurs following transfusion of normal erythrocytes to patients in whom abnormal hemolytic processes are operating. In these circumstances the cells are destroyed indiscriminately, without respect to their age. These two types of destruction of erythrocytes are illustrated by the hypothetic graph of chart 1.

ˈBrown and associates[6] demonstrated that in simple anemias, such as the so-called idiopathic hypochromic type, nearly all transfused cells were destroyed by a linear process. In acquired hemolytic anemia and after burns, on the other hand, as many as 70 per cent of the cells were destroyed by an exponential mechanism. In other anemias intermediate
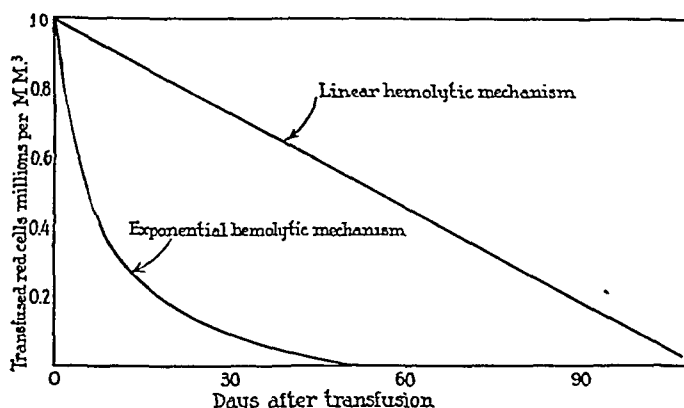

Chart 1.—Hypothetic destruction of transfused erythrocytes by normal (linear) and abnormal (exponential) hemolytic mechanisms (after Brown, Hayward, Powell and Witts[6]).

results were obtained, and in 2 cases a shortened life of the erythrocytes after transfusion was associated with a linear type of decay. It therefore appeared that the manner in which patients disposed of donated cells threw some light on the pathogenesis of their anemia.

Dacie and Mollison[4] found that normal cells had a normal survival time when given to 5 patients with congenital hemolytic jaundice.

of the Erythrocytes, J. A. M. A. **102:**1779-1780 (May 26) 1934. Wiener, A. S., and Schaefer, G.: Limitations in the Use of Preserved Blood for Transfusion, M. Clin. North America **24:**705-722 (May) 1940. Denstedt, O. F.; Osborne, D. E.; Stansfield, H., and Rochlin, I.: The Survival of Preserved Erythrocytes After Transfusion, Canad. M. A. J. **48:**477-486 (June) 1943. Callender, S. T.; Powell, E. O., and Witts, L. J.: The Life Span of the Red Cell in Man, J. Path. & Bact. **57:**129-139 (Jan.) 1945.

6. Brown, G. M.; Hayward, O. C.; Powell, E. O., and Witts, L. J.: The Destruction of Transfused Erythrocytes in Anemia, J. Path. & Bact. **56:**81-94, 1944.

However, blood taken from 1 of the patients before splenectomy was completely eliminated within fourteen days after transfusion to another person. Normal blood given to the same recipient at the same time survived normally. Erythrocytes taken from the same patient a year after splenectomy likewise disappeared rapidly from the circulation of a normal recipient following transfusion. In the opinion of the authors, these results indicated that the fundamental defect in this disease is the formation of fragile red cells and that this defect persists after splenectomy.

Similar observations were reported by Dacie and Mollison in a case of chronic hemolytic anemia with nocturnal hemoglobinuria. Although an increased rate of destruction of the patient's own cells was evident, transfused normal cells survived normally in the patient's circulation. It was believed that this result supported the view expressed by Ham [7] that the basic abnormality in this disorder is likewise in the erythrocytes, rather than in the serum, spleen or the reticuloendothelial system.

In the first case to be described in this report autologous cells as well as donated normal cells were rapidly destroyed in the patient. This suggested an abnormality of the erythrocyte-destroying mechanism. In the second case transfused normal cells disappeared from the patient's circulation at a normal rate, but the patient's cells were rapidly destroyed after transfusion to a child. Furthermore, the patient's plasma had no hemolytic effect on the cells of a normal recipient. These observations suggested that the abnormality in this case was in the erythron.

The objectives of this report are as follows:

1. To describe in detail the clinical course in 2 unusual cases of hemolytic anemia, both of which might be labeled "acquired" or "atypical" and 1 of which responded to splenectomy.

2. To demonstrate the utility of transfusion experiments in localizing hemolytic abnormalities.

3. To describe the behavior of two irregular agglutinins which may have been responsible for some of the manifestations of the first case.

METHODS

The methods of determining the hematocrit values,[8] the per cent of reticulocytes,[2] acid hemolysis [7] and mechanical fragility [9] of erythrocytes, the serum

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7. Ham, T. H.: Studies on Destruction of Red Blood Cells: I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; an Investigation of the Mechanism of Hemolysis, with Observations on Five Cases, Arch. Int. Med. **64:** 1271-1305 (Dec.) 1939.

8. Wintrobe, M. M.: Macroscopic Examination of the Blood, Am. J. M. Sc. **185:**58-71 (Jan.) 1933.

bilirubin [10] and fecal urobilinogen concentrations,[11] the Donath-Landsteiner reaction [12] and the presence or absence of autohemolysins and isohemolysins [13] are described elsewhere.

The technics used in tests for osmotic fragility, autoagglutination, isoagglutination and differential agglutination of autologous and of transfused cells will be described subsequently.

REPORT OF CASES

CASE 1.—L. B., a 61 year old white woman, had appeared slightly pale and jaundiced since 1941 but was essentially free of symptoms until late December 1943, when weakness and dizziness were first noted. At that time the patient suddenly became very pale and icteric and was given liver extract and iron, without effect. She was admitted to the Highland Hospital of Rochester, N. Y., on Feb. 25, 1944, at which time the red blood cell count was 1,300,000. The count rose to 3,900,000 after eight transfusions of whole blood, but it soon declined to the original value. The patient was discharged from the Highland Hospital on March 12, 1944. She was readmitted on March 24 for two more transfusions and then was transferred to the Strong Memorial Hospital for further study on March 30.

Family History.—The family history was noncontributory, and detailed examinations of the blood of·the patient's two children did not reveal any abnormalities.

Observations on Admission.—The temperature was 102 F., pulse rate 120, respiration rate 30 and blood pressure 118 systolic and 62 diastolic. The patient appeared acutely ill and apprehensive. The skin and mucous membranes were extremely pale, and the skin and scleras were moderately icteric. The heart was slightly enlarged, and there was a systolic, probably hemic, murmur over the entire precordium. The liver and spleen were palpable 4 and 8 cm., respectively, below the costal margin. There was 1 plus pitting edema about the ankles.

Laboratory Observations.—On admission laboratory observations were as follows: red blood cells 1,290,000, hematocrit value 12.3 per cent, hemoglobin value 3.5 Gm. per hundred cubic centimeters; white blood cells 7,450, platelets 132,000 and reticulocytes 33 per cent. The differential count of the leukocytes was normal. There were slight poikilocytosis and moderate anisocytosis of the red cells; the average size of the cells was considerably above normal, and most of the macrocytes were polychromatophilic. Spherocytes and nucleated red cells were not present; search for the former was repeatedly made in wet preparations. Tests for warm and cold hemolysis (Donath-Landsteiner), acid hemolysis (Ham) and sickling yielded·negative results. The icterus index was 24, bilirubin (direct test)

9. Shen, S. C.; Castle, W. B., and Fleming, E. M.: Experimental and Clinical Observations on Increased Mechanical Fragility of Erythrocytes, Science **100**:387-389 (Oct. 27) 1944.

10. Malloy, H. T., and Evelyn, K. A.: Oxidation Method for Bilirubin Determinations in Bile and Meconium with the Photoelectric Colorimeter, J. Biol. Chem. **122**:597-603 (Feb.) 1938.

11. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458-475 (Sept.) 1936.

12. MacKenzie, G. M.: Paroxysmal Hemoglobinuria, Medicine **8**:159-191 (May) 1929.

13. Dameshek, W.: The Management. of Acute Hemolytic Anemia and the Hemolytic Crisis, Clinics **2**: 118-165, 1943.

1.28 mg., bilirubin (indirect test) 3.64 mg. and nonprotein nitrogen 45 mg. per hundred cubic centimeters, albumin 3.6 Gm., globulin 2.9 Gm. and fibrinogen 0.338 Gm. per hundred cubic centimeters.

Examinations of the urine consistently showed traces of albumin, large amounts of urobilinogen (qualitative tests) and many yellow-brown granular casts. At no time did the patient have hemoglobinemia or hemoglobinuria. Quantitative determinations of fecal and urinary urobilinogen excretion were not obtained. The blood was cultured twice, with negative results. The stool contained no blood, ova or parasites. Wassermann and Kahn reactions were negative.

Course.—The most important events of the patient's stay in the hospital are indicated in chart 2. Febrile reactions had occurred after at least six of the ten transfusions given at the Highland Hospital, and chills and fever followed nearly all twenty transfusions administered at the Strong Memorial Hospital. At no
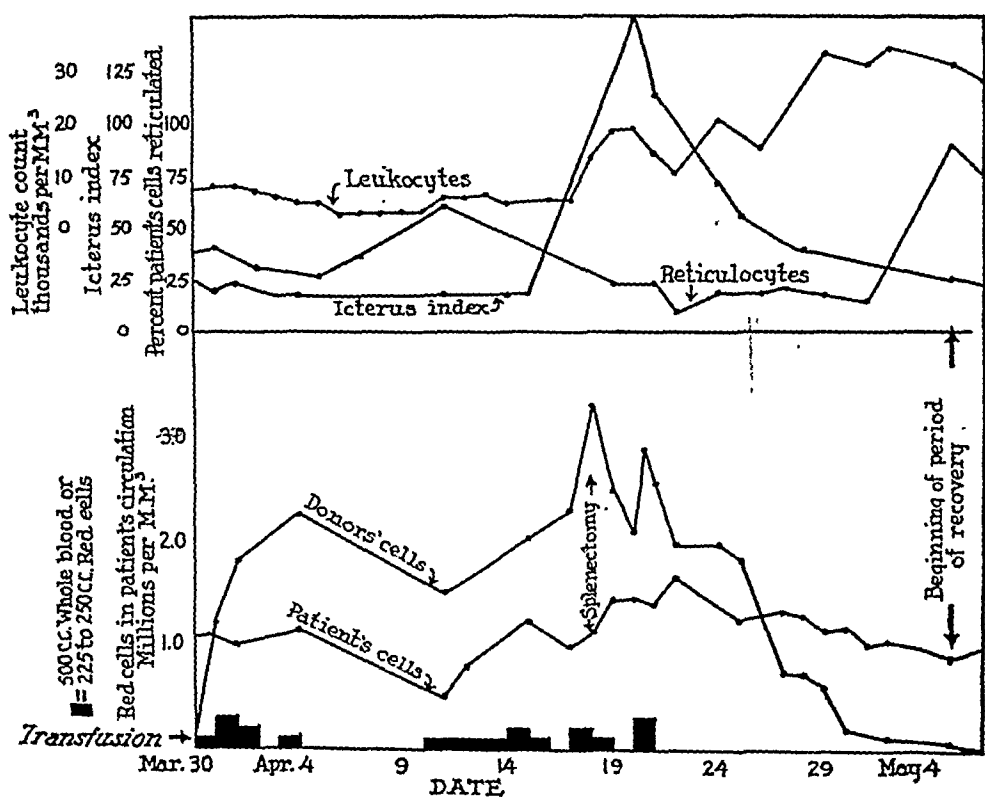

Chart 2 (case 1).—Hematologic changes during patient's hospital stay.

time was the patient completely afebrile, but there was a minimum of fever during the period from April 4 to 9, when no transfusions were given. Rapid destruction of all donated cells as well as of the patient's own red cells was demonstrated by differential agglutination studies, which will be described separately. Because of the rapid elimination of cells, transfusions provided only temporary benefit.

Splenectomy was performed by Dr. J. J. Morton on April 18. The spleen weighed 1,160 Gm.; it was firm and dark red, and six areas of infarction were present. Microscopic examination of the spleen revealed many red cells and collections of dark pigment granules in the venous sinuses. There was hyperplasia in the malpighian bodies, especially in the germinal centers, but no evidence of erythrophagocytosis could be found.

Postoperative Complications.—The early postoperative course was stormy and was marked by rapid destruction of red cells and the development of congestive

heart failure. The icterus index rose to a peak of 150 on April 20, at which time the foam test of the urine elicited a positive reaction for bilirubin, and the serum bilirubin concentration was 9.24 mg. per hundred cubic centimeters direct and 14.7 mg. per hundred cubic centimeters indirect.

The patient was rapidly digitalized on April 20 because of the development of auricular fibrillation and congestive heart failure. A transfusion of 750 cc. of red cells was given slowly on the same day. These measures were followed by temporary improvement, but during the next ten days the course was rapidly downhill and was marked by leukocytosis, hectic fever and phlebothrombosis of several of the superficial veins of the legs. Thrombosis of the splenic vein was also suspected. Additional transfusions were not given because the patient's serum agglutinated cells of all groups at body temperature. At the time of discharge from the hospital on May 2 the prognosis appeared to be grave. On May 5, when a visit was made at the home, the red cell count had fallen to 880,000, and it was demonstrated that nearly 90 per cent of the patient's cells were reticulocytes.

Phase of Recovery.—After May 5 there was steady objective and subjective improvement. The gradual rise of the red cell count and the decrease in mean
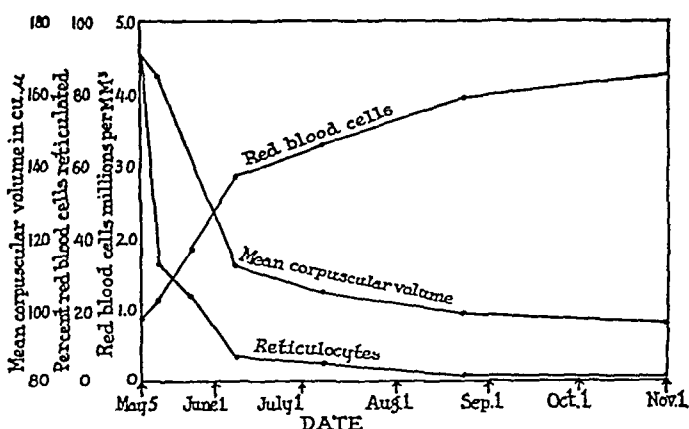

Chart 3 (case 1).—Relation of total erythrocyte count, reticulocyte count and mean corpuscular volume during phase of recovery. Note parallelism between mean corpuscular volume and per cent reticulocytes.

corpuscular volume and in the number of reticulocytes are shown graphically in figure 3. The patient was performing all the usual household duties when last seen, on Oct. 31, 1944. At that time all hematologic values were normal except for the persistence of cold hemagglutinins. Her condition in June 1945 remains good.

Fragility of Erythrocytes.—Fragility of the red cells in hypotonic solutions of sodium chloride was determined on five occasions. Tests were made in two ways. The customary method involved placing 1 drop of oxalated blood [14] into each of a series of tubes containing 1 cc. of saline solution in concentrations ranging from 0.80 per cent to 0.20 per cent. After the contents were mixed, the tubes were placed in the refrigerator overnight and checked grossly for hemolysis the following day. Record was made of the concentration of salt in the first tubes in the series

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14. When the plasma was icteric, as in this case, the cells were washed and resuspended with an equal volume of isotonic solution of sodium chloride. The cells of the control blood were treated in the same way.

in which hemolysis was (1) detectable, (2) marked and (3) complete. The readings for normal blood tested in this way were: (1) 0.46 to 0.50 per cent, (2) 0.38 to 0.42 per cent and (3) 0.30 to 0.34 per cent.

On each occasion fragility was also tested by a slight modification of the photoelectric method of Hunter.[15] Ten cubic centimeters of salt solution were placed in each of a series of Evelyn colorimeter tubes, and 0.02 cc. of blood was added to each with a hemoglobinometer pipet. After standing thirty minutes at room temperature the tubes were centrifuged fifteen minutes at 1,500 revolutions per minute. The tubes were then carefully moved to the colorimeter, where the concentration of hemoglobin in the supernatant fluid was determined.

On March 31 and April 3 fragility was somewhat increased. Hemolysis began at 0.69 and 0.56 per cent, respectively, and was marked at 0.48 per cent and complete at 0.32 per cent on both dates. Results with the colorimetric method also indicated that fragility was increased in concentrations of salt between 0.50 and 0.64 per cent. On April 18 and 28 and on May 22 fragility, tested by both methods, was normal.

The mechanical fragility of the cells from this patient was not determined.

Destruction of Transfused Cells.—The fate of erythrocytes donated to this patient was followed closely by means of quantitative differential agglutination tests. The technic employed was that of Ashby[3] as modified by Dacie and Mollison,[4] except that the dilution of the recipient's cells in the initial suspension was 1:101 instead of 1:51. Each mixture of serum and cells was prepared in duplicate, and a separate count of the unagglutinated cells in each tube was made by each of two persons. The count finally recorded was therefore the average of four separate counts of each serum-cell mixture. Total red cell counts were also made in duplicate by two persons and the average of the four counts recorded. Further details of the Ashby technic, as employed in this laboratory, are given elsewhere.[2]

The patient's blood group was A₂MRh+; this was repeatedly confirmed during the convalescent period after all of the donated cells had been eliminated. All but three of the donors were Rh positive.[16] The blood groups of the donors were as follows:

Group	Number of Donors
A₁	21
A₁MN	16
A₁M	4
A₁N	1
A₂	6
A₂MN	4
A₂M	1
A₂N	1
O	3
OMN	1
OM	2
	30

The donations of A₁M and A₂M blood had been given before the patient was transferred to the Strong Memorial Hospital, and these cells had been destroyed by the time the series of differential agglutination tests was begun.[17] Thereafter,

15. Hunter, F. T.: A Photoelectric Method for the Quantitative Determination of Erythrocyte Fragility, J. Clin. Investigation **19**:691-694 (Sept.) 1940.

16. Anti-Rho′ human serum was used for all the Rh tests referred to in his paper. Wiener, A. S.: The Rh Blood Factors, J. A. M. A. **127**: 294 (Feb. 3) 1945.

group A blood was removed from the bank and given to the patient only if it belonged to type N or MN.

When anti-N serum was added to suspensions of the patient's cells after transfusion of N or MN blood, the donated cells were agglutinated while the patient's cells remained unagglutinated. The latter, free cells, were readily counted after the serum-cell mixture was transferred to a counting chamber. A correction factor of 30,000 cells per cubic millimeter had to be included in the calculations, because this was the average number of cells left unagglutinated after addition ·of anti-N serum to suspensions of N and MN cells unmixed with M cells. Calculations were carried out according to the following equations:

$$\text{Number of patient's cells} = \text{number cells unagglutinated by anti-N serum} - 30{,}000$$
$$\text{Number donated N or MN cells} = \text{total red cell count} - \text{number of patient's cells.}$$

On April 20, 1944, two days after splenectomy, the patient was given 750 cc. of fresh group O red cells pooled from three donors (OM .and OMN). The survival of these cells was studied by the use of B serum, which agglutinated the patient's A_2 cells and the donated A_1 cells (only A_1 cells had been transfused since March 31) and left the O cells unagglutinated. The following calculation was then employed:

$$\text{Number of donated O cells} = \text{number cells unagglutinated by B serum} - 15{,}000.$$

It was necessary to subtract 15,000 cells per cubic millimeter in this, equation, because this was the number of cells unagglutinated by B serum before transfusion.

Since absorbed B serum agglutinates A_1 cells but not A_2 cells or O cells, the number of A_2 cells (patient's own cells) present after transfusion of O cells was determined as follows:

$$\text{Number } A_2 \text{ (autologous) cells} = \text{number cells unagglutinated by absorbed B serum} - 35{,}000 - \text{number donated O cells.}$$

A correction of 35,000 cells was made because this was the average number of cells left unagglutinated after absorbed B serum was added to A_1 cells (pooled from the last three A_1 donors used) unmixed with A_2 or O cells. The absorbed · B serum had been prepared by absorbing with A_2 cells a very potent B serum from a donor who had been immunized with A and B specific substances.[18]

Once the numbers of O and A_2 cells were estimated, calculation of the number of A_1 cells present was carried out according to the following equation:

$$\text{Number of } A_1 \text{ cells} = \text{total red cell count} - \text{number of O cells} - \text{number of } A_2 \text{ cells.}$$

It is obvious that ·the numbers of O, A_2 and A_1 cells present at any given time after transfusion can be only roughly estimated by these calculations. Nevertheless, counts made in quadruplicate every twenty-four to forty-eight hours yielded results which showed clearly the trend of cell destruction.

The numbers of autologous and total donated cells present at each point during the patient's hospital stay are shown in chart 2. The number of autologous cells ranged from 490,000 to 1,700,000. The latter figure was reached after the last

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17. The A_2M cells were transfused a month prior to the patient's transfer. Because they were of the same type as the patient's, their destruction could only be assumed, but this seemed a fair assumption in view of subsequent observations. Destruction of the A_1M cells was demonstrated by the use of absorbed B serum.

18. Young, L. E., and Witebsky, E.: Studies of the Subgroups of Blood Groups A and AB: II. The Agglutinogen A_3; Its Detection with Potent B Serum and a Study of Its Inheritance, J. Immunol. **51**:111-116 (Aug.) 1945.

series of transfusions, and it coincided with a sharp drop in the proportion of the patient's cells which were reticulated.[19] This fact suggests that the transfusions affected the marrow in such a way that more mature (and less readily destroyed?) cells were released into the circulation. One might also argue that when large numbers of donated cells were in the patient's circulation fewer autologous cells were destroyed per unit of time, simply because there was some limit to the patient's total hemolytic capacity. At any rate, it is clear that both donated and autologous cells were destroyed by this patient at a rapid rate.

Chart 4 shows in more detail the picture of erythrocyte destruction during the first fifteen days following the large transfusion of O cells. It is apparent that both A_1 and O cells disappeared from the patient's circulation at a rapid rate and that the number of autologous cells showed a significant decline during this same period.

Reticulocytosis and Macrocytosis.—It is also noted (charts 2 and 3) that during the latter part of this period, when the total red cell count had fallen below
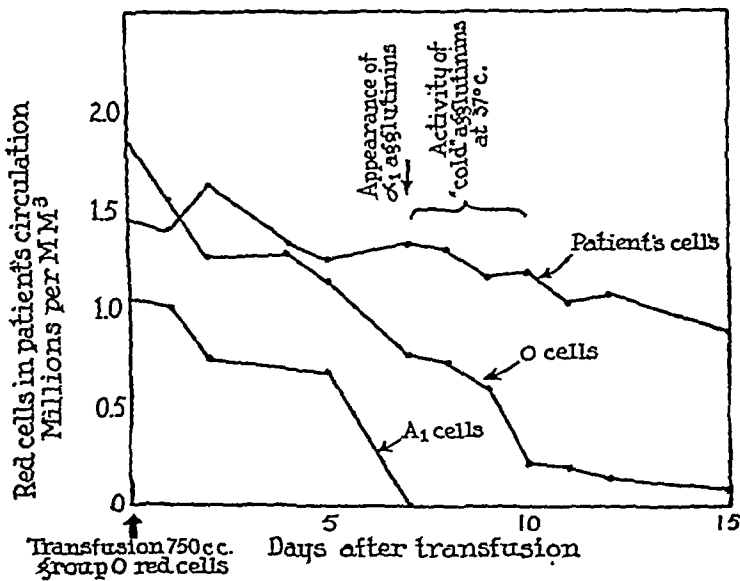

Chart 4 (case 1).—Disappearance of O, A_1 and autologous cells following last transfusion on April 20.

1,000,000, there was a sharp rise in the percentage of the patient's cells which were reticulated. On May 5 the total erythrocyte count was 880,000, of which 80,000 were O cells. The reticulocyte count on this date was 82 per cent, and it was calculated that approximately 90 per cent of the patient's own cells were reticulocytes. During the next month the patient made astonishing clinical improvement and the erythrocyte count rose to nearly 3,000,000 while the reticulocytes fell to 6 per cent. Thereafter, there was a slow but steady return to normal of the entire blood picture.

19. The proportion of the patient's cells which were reticulocytes was calculated by assuming that all reticulocytes present were autologous cells; for practical purposes this assumption was justified. The calculation was as follows:

Per cent patient's cells reticulated = per cent total
red cells reticulated $\times \dfrac{\text{total red cell count}}{\text{patient's red cell count}}$.

It is evident in chart 3 that the decrease in reticulocytes during the period of recovery was closely parallel to the decrease in mean corpuscular volume of the erythrocytes. This striking parallelism suggests that the macrocytosis noted during the acute phase of the illness was due largely, if not entirely, to reticulocytosis. Dameshek and Schwartz [20] have referred to this type of macrocytosis as "pseudo" or "polychromatic" in contrast to the orthochromatic macrocytosis of untreated pernicious anemia.

Irregular Agglutinins in Case 1.—Alpha$_1$ (a_1) Agglutinins: Between March 1 and April 18 this patient (blood subgroup A$_2$) received a total of twenty-one transfusions from donors belonging to subgroup A$_1$. Alpha$_1$ ((a_1) agglutinins, active against A$_1$ cells at room temperature (chart 4), were first detectable on April 27 (titer 1:4). A maximal titer of 1:16 was reached on April 30, and this was followed by a gradual decline in potency (titer 1:4 on August 24; no agglutination of A$_1$ cells on October 31).

On several occasions it was possible to demonstrate activity of a_1 agglutinins at 37 C. in fresh serum from which the cold agglutinins had been removed, as described subsequently. In spite of this observation, it was believed that the rapid destruction of A$_1$ cells (chart 4) could not be attributed in any great measure to the action of a_1 agglutinins, because O cells, and probably autologous cells, were being destroyed at nearly the same rate during this period.

Cold Hemagglutinins: Throughout the entire period of observation of this patient (seven months) cold hemagglutinins were demonstrable in the serum in relatively constant amounts. The properties of these antibodies were studied in some detail.

Titrations were carried out by mixing 0.2 to 0.5 cc. of serum in serial twofold dilutions with equal volumes of 1 per cent suspensions of cells which had been washed three times with saline solution. The serum-cell mixtures were allowed to stand two hours at room and body temperatures and two or more hours at refrigerator temperature. They were then examined both grossly and microscopically for the presence or absence of agglutination. Titers were recorded in terms of the final dilution of serum after addition of the suspension of cells; that is, the first tube containing undiluted serum plus an equal volume of suspension of cells was recorded as diluted 1:2.

The method ordinarily used in this laboratory for titration of cold hemagglutinins is fully discussed in a separate paper.[21] During the study of case 1 the only noteworthy deviation from the usual technic was that of reading the end points microscopically instead of grossly. This was done by quickly transferring a drop of the serum-cell mixture to a plain glass slide for examination under the low power of a microscope. The microscopic readings were considered necessary in order to detect minor degrees of agglutination in absorption experiments. Agglutination graded 1 plus to 4 plus was visible grossly, while that graded plus-minus was detected only with the microscope.

Agglutinin-Absorption Studies: Although numerous agglutinin-absorption tests were performed, only one will be described in detail as a typical example. On June 6, 1944, 8 cc. of fresh defibrinated blood (hematocrit value 32 per cent) was placed in a large tightly stoppered test tube, which was then completely surrounded with cracked ice in a beaker. The beaker was placed in a refrigerator

20. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231-327 (May) 1940.

21. Young, L. E.: The Clinical Significance of Cold Hemagglutinins, Am. J. M. Sc. **211**:23-39 (Jan.) 1946.

at 4 C. for six hours. At the end of this period the tube was quickly packed in finely chipped ice in the carrier of a centrifuge and spun at 1,500 revolutions per minute for three minutes. The serum, from which the cold agglutinins had been largely absorbed, was then removed with a sterile drawn-out pipet and set aside for titration. Throughout the entire procedure, every effort was made to prevent warming of the tube.

After most of the serum had been removed, the cells were washed twice with equal volumes of isotonic solution of sodium chloride which had been chilled to 1 C. The cold agglutinins were then eluted from the cells by adding an amount of warm (37 C.) saline solution equal to that of the serum removed. After the mixture of cells and saline solution had stood at 37 C. for one hour, the tube was surrounded with warm (40 C.) water in the carrier of a centrifuge and spun at 2,000 revolutions per minute for ten minutes. The "eluate" containing the cold agglutinins was then removed with a sterile drawn-out pipet and set aside for titration.

Unabsorbed serum used in this and in other tests was separated from clotted (or defibrinated) blood by centrifugation at 2,000 revolutions per minute for ten minutes after incubation at 37 C. for one hour. This serum, the absorbed serum and the eluate were titrated with autologous A_1, A_2 and O cells on June 7, 1944. The tubes were examined after standing at room temperature for two hours and again after being warmed in a water bath at 37 C. for two hours. They were then placed in the refrigerator at 4 C. overnight and examined again on the following morning.

The results of this experiment are shown in table 1. The absorption of cold agglutinins has been described by a number of observers [22] but was of particular interest in this case because it served to separate the cold agglutinins from the a_1 agglutinins. It is clear from results with the absorbed serum that the cold agglutinins were largely removed while the a_1 agglutinins active against A_1 cells were relatively undisturbed. A prozone was noted when the absorbed serum was tested with autologous cells at 4 C. This was invariably observed in repeated experiments in which the patient's serum was absorbed with autologous and washed A_1, A_2 and O cells and then tested with autologous cells.

Thermal Amplitude of Agglutinins: Although the titer (1:32 to 1:64 with O cells and 1:64 to 1:128 with autologous cells) of cold agglutinins at 4 C. remained nearly constant throughout the period of study, the thermal amplitude of these antibodies fluctuated widely. Prior to April 27, 1944, no activity at room or body temperatures could be demonstrated. On that date, however, there was great difficulty in counting red cells because of slight agglutination, even when the diluting fluid was warmed to 37 C. It was also found that the patient's freshly drawn serum weakly agglutinated not only autologous cells but also other A_2 cells and A_1 and O cells at 37 C. and strongly agglutinated these cells at 22 C. Activity of these antibodies at body temperature persisted until May 1, 1944, after which date there was a gradual decline in activity at the warmer temperatures.

During the period April 27 to May 1 and thereafter serums that had been stored for periods of only one or two days agglutinated only A_1 cells at room temperature and showed no activity at 37 C. A table showing the titers against A_1, A_2 and O cells at refrigerator and at room temperature throughout the entire period of observation is presented in a separate paper.[1] Serum drawn on April 28

22. Stats, D., and Wasserman, L. R.: Cold Hemagglutination: An Interpretive Review, Medicine **22**:363-424 (Dec.) 1943.

and tested with B cells the following day gave titers of 1:128, 1:64 and 1:32 at 4, 24 and 37 C., respectively.

It is evident in table 1 that the eluate prepared on June 6, 1944, showed greater activity at warmer temperatures than did the serum from which it was prepared.

TABLE 1.—*Typical Results of Titration of Serum and Eluate with Various Cells at Refrigerator, Room and Body Temperatures: Separation of a_1 and Cold Agglutinins by Absorption, Case 1*

Serum or Eluate	Cells	Temp. of Test, C.	Degree of Agglutination Produced by Given Dilution of Serum or Eluate							
			1:2	1:4	1:8	1:16	1:32	1:64	1:128	
Serum drawn 6/6/44 unabsorbed	Autologous (A2)	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	+++±	+++	+++	++	+	+	±	
	A1	22	++	+	—	—	—	—	—	}Agglutination of A1 cells at 22 C. due to a_1 agglutinins
		37	—	—	—	—	—	—	—	
		4	+++±	+++	++	+±	+	±	—	
	A2	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	+++	+++	++	+±	+	+'	—	}Agglutination of all cells at 4 C. due to cold agglutinins
	0	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	+++	+++	++	+±	+	±	—	
Serum drawn 6/6/44 absorbed with autologous cells	Autologous	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	}Prozone with autologous cells
		4	±	±	+	+±	+	±	—	
	A1	22	+	±	—	—	—	—	—	
		37	—	—	—	—	—	—	—	}Minimal absorption of a_1 agglutinins
		4	+±	+	—	—	—	—	—	
	A2	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	±	—	—	—	—	—	—	}Marked absorption of cold agglutinins
	0	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	±	—	—	—	—	—	—	
Eulate 6/6/44 from autologous cells	Autologous	22	+	±	—	—	—	—	—	
		37	+	—	—	—	—	—	—	
		4	++	++	+±	+	+	±	—	
	A1	22	+	±	—	—	—	—	—	Greater activity of cold agglutinins in eluate at higher temperatures suggests release from inhibitory effect of serum
		37	+	—	—	—	—	—	—	
		4	++	+±	+	+	±	—	—	
	A2	22	+	±	—	—	—	—	—	
		37	±	—	—	—	—	—	—	
		4	++	+±	+	+	±	—	—	
	0	22	+	±	—	—	—	—	—	
		37	+	—	—	—	—	—	—	
		4	++	+±	+	+	±	—	—	

This phenomenon was noted in repeated experiments of similar type, in which fresh or one day old unabsorbed serum failed to agglutinate cells at room or body temperature while eluates prepared from the same serum showed weak but definite activity at these temperatures. This could not be demonstrated in eluates that had been stored in the refrigerator for more than a week or in eluates prepared from serum stored more than a few days.

These observations suggested that the patient's serum might contain some substance which inhibited activity of the cold agglutinins at warmer temperatures. This possibility was further explored by the following experiment: An eluate

prepared from fresh defibrinated blood on Aug. 24, 1944, by the same technic as that used with the specimen of June 6, was tested on August 25. The results were almost exactly like those shown in table 1. This eluate was tested again with autologous and A₁ cells on August 28. In each of four tubes was placed 0.2 cc. of eluate, to which 0.2 cc. of 1 per cent suspension of washed cells was added, as follows: to tube 1, autologous cells suspended in isotonic solution of sodium chloride; to tube 2, autologous cells suspended in absorbed serum[23]; to tube 3, A₁ cells suspended in saline solution, and to tube 4, A₁ cells suspended in absorbed serum.[23]

The tubes were examined after incubation at 37 C. for two hours and again after standing overnight at 22 C. They were then checked once more after a second incubation at 37 C. for two hours. The results are given in table 2 and indicate that the patient's serum had some inhibitory effect on agglutination. Similar results were obtained in three additional experiments of this type (also using A₂ and O cells), but when the cells were suspended in serum from normal persons the results were equivocal.

Determinations of thermal amplitude and absorptive characteristics of the patient's serum were made in duplicate with fresh, noninactivated serum and with serum heated at 56 C. for thirty minutes. The results were essentially the same.

The patient's serum drawn on Oct. 31, 1944 was absorbed with autologous and with O cells at 37 C. and then tested with autologous, A₁, A₂ and O cells at

TABLE 2.—*Inhibitory Effect of Serum on Agglutination at Warmer Temperatures, Case 1*

Temperature, C.	Autologous Cells in		A₁ Cells in	
	Saline Solution	Absorbed Serum	Saline Solution	Absorbed Serum
37	±	—	±	—
22	+	±	+±	+
37	±	—	+	—

4, 22 and 37 C. The reactions indicated that neither antibodies nor inhibitory substances had been removed by "warm" absorption.

Attempts to define more completely the inhibitory property of the patient's serum were unsuccessful for three reasons: 1. It was impossible to obtain large quantities of serum and eluate. 2. Eluates deteriorated rapidly with storage. 3. Agglutination at the warmer temperatures was weak and often difficult to evaluate.

CASE 2.—M. G., a white woman, was 40 years of age when first admitted to the Strong Memorial Hospital, Oct. 3, 1929. She had had jaundice in association with a febrile illness at the age of 10 and had felt exhausted for several months in 1925 and 1927 but otherwise had been in good health until July 1929, when she began to suffer increasing fatigability, dizziness, numbness and tingling of the hands and anorexia. She had become pregnant in June 1929.

Family History.—The family history disclosed nothing of significance with respect to jaundice and anemia. Complete examinations of the blood of the patient's brother, sister and daughter failed to reveal any abnormalities. These examinations included study of wet preparations for the presence of spherocytes and tests of the fragility of the red cells in hypotonic saline solution.

23. The patient's serum was absorbed with autologous cells on August 24.

Physical Examination.—On the first admission the physical examination revealed normal vital signs. The patient was well developed and moderately obese. The skin and scleras were slightly icteric and the mucous membranes moderately pale. There was no glandular enlargement, and the liver and spleen were not palpable.

Laboratory Observations.—The red blood cell count was 2,960,000; white cell count 9,600, with a normal differential distribution, and hemoglobin value, 11.3 Gm. per hundred cubic centimeters. Reticulocytes varied from 8 to 16 per cent. There were moderate poikilocytosis and pronounced anisocytosis of the red cells; many of the larger cells showed basophilic stippling or polychromatophilia. Repeated tests of the fragility of the red cells in a hypotonic solution of sodium chloride were made by the customary method, with normal results. Platelets were present in normal numbers. The icterus index was 10. The only significant result of urinalysis was a strongly positive qualitative reaction for urobilin. There was no free hydrochloric acid in a fasting specimen of gastric contents. The patient could not retain the tube for additional examinations. Roentgenograms of the gastrointestinal tract and of the skull showed nothing abnormal. Wassermann and Kahn tests elicited negative reactions.

Course.—The patient was discharged from the hospital after completion of the aforementioned procedures but was later readmitted on four occasions for further study. Examinations of the blood were made on numerous visits to the hematologic laboratory. She gave birth to a normal girl by cesarean section on March 6, 1930, and a transfusion of 500 cc. of whole blood was given at that time without reaction.

Liver extract and iron were administered periodically from October 1929 until April 1932, without any beneficial effect. The patient's liver was first palpated with certainty in 1936 and the spleen in 1940; both organs have since remained 3 to 5 cm. below the costal margin. The red blood cell count gradually fell to a level of about 2,000,000 in 1942 and has remained near that figure. Since 1942 the hemoglobin has varied from 8.5 to 9.5 Gm. per hundred cubic centimeters, the hematocrit value from 28 to 29 per cent and the icterus index from 15 to 25. The white cells and platelets have remained normal. Prior to November 1942, the highest reticulocyte count recorded was 23 per cent, but since that date the counts have been consistently between 45 and 73 per cent (except after transfusions). The mean corpuscular volume of the red cells rose from a value of 118 when first determined, in 1939, to values of 135 to 150 during the period from 1942 to 1944. Spherocytes and nucleated red cells have never been observed in the peripheral blood, although numerous smears and wet preparations have been examined.

In 1942 and 1943 tests for the following reactions were carried out on three separate occasions with negative results: cold hemagglutination, warm and cold (Donath-Landsteiner) hemolysis, acid hemolysis (Ham) and sickling.

Since 1929 the patient has tired easily and has had frequent dizzy spells, but she managed to carry on work as a clerk, until June 9, 1944, when hospitalization was necessary because of cerebral thrombosis. She has since been in bed or in a chair most of the time. The transfusion experiments to be described were performed between the dates of June 12 and Nov. 13, 1944. The patient was in the hospital from June 9 to July 15 and from October 4 to 6, 1944. Splenectomy was contemplated on a number of occasions since 1929 but was not performed.

Fragility of Erythrocytes.—When tested by the customary method, the red cells of this patient appeared to have normal fragility in hypotonic solutions of sodium chloride. Repeated determinations were made in 1942, 1943, and on June 12, Oct. 17 and Nov. 13, 1944. On the last three dates tests were also carried out by the photoelectric technic previously described. By the latter method there appeared to

be a substantial increase in fragility in solutions with concentrations of salt between 0.40 and 0.64 per cent.

The mechanical fragility [24] of the cells of this patient was tested by a technic similar to that recently 'described by Shen, Castle and Fleming.[9] Blood was drawn into a mixture of potassium and ammonium oxalates and the hematocrit value adjusted to 40 per cent. A 1 cc. sample was then placed in a stoppered 125 cc. Erlenmayer flask containing 20 glass beads. The flask was attached to the periphery of a wheel 15 cm. in diameter and revolved at 24 revolutions per minute for two hours at room temperature. Samples were taken at one hour and two hours and the per cent of hemolysis determined.

The average figure for mechanical fragility was 5.3 per cent at one hour and 10.6 per cent at two hours for 15 normal, or nonanemic, controls. The patient's mechanical fragility was 18.8 per cent at one hour and 23.7 per cent at two hours on March 30, 1945 and 9 per cent and 22.6 per cent at one and two hours, respectively, on April 6, 1945. The normal values obtained were higher than those reported by Shen and associates, probably because of technical factors. Nevertheless, the fragility of the patient's cells to mechanical stress was much greater than that of any of the normal subjects tested.

It is possible that the apparently increased osmotic fragility of the patient's cells when tested by the colorimetric method was due to the trauma of centrifugation, since normal results were obtained by a method not involving centrifugation. This possibility is being investigated.

Transfusion Studies.—Survival of Transfused Normal Cells in Patient's Circulation: On June 12, 1944, 350 cc. of blood was removed from the patient, and the phlebotomy was immediately followed by a transfusion of 750 cc. of normal, fresh red cells given through the same needle.

The patient's blood group was OMNRh+. The blood group of all the three donors who contributed the normal cells was ONRh+. When anti-M serum was added to suspensions of the patient's cells after transfusion, the patient's own cells were agglutinated while the donated cells remained unagglutinated and could be counted in the usual way. By means of the technic previously described it was possible to determine the number of donated cells present in the patient's circulation at various intervals following the transfusion.

The results of this experiment are shown in chart 5, in which the gradual loss of donated cells over a period of more than one hundred days is evident. The number of autologous cells, calculated by subtracting the donor's cell count from the total red cell count, dropped to 1,690,000 after the phlebotomy and transfusion and then rose to a peak of 2,200,000 on the fourteenth day.

The proportion of the patient's own cells which were reticulocytes [19] declined rapidly during the first month after transfusion. There was also a sharp decrease in the excretion of fecal urobilinogen at this time.[25] These findings, together with the elevated count of autologous cells during this period, indicate that the transfusion had caused a decline in the rate of destruction of autologous cells and that more mature cells were being released from the marrow. Similar changes were described following transfusion in case 1 and were apparent to a lesser extent after the second transfusion in case 2 (to be described; see chart. 5).

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24. The tests for mechanical fragility were carried out in the laboratory of Dr. Marion Emerson.

25. Difficulty was encountered in collection of feces from this patient. However, this difficulty was not sufficiently great to alter the interpretation of the results. Dr. Samuel H. Bassett and Miss Helen Schantz assisted in the determinations of the urobilinogen.

On Oct. 5, 1944, one hundred and fifteen days after the first phlebotomy and transfusion, 550 cc. of blood was removed from the patient. Immediately after this second phlebotomy, 500 cc. of normal red cells of group ONRh+ were transfused through the same needle. There was no untoward reaction after any of these procedures. Between October 5 and November 13 it was possible to check the patient's blood counts only four times. However, it was evident that the normal donated cells were again destroyed rather slowly and that transfusion had once more caused a decline in reticulocytes (figure 5).

Rapid Destruction of Patient's Cells After Transfusion to a Small Child: From the 550 cc. of citrated blood drawn from the patient on October 5, 150 cc. of red cells was obtained and transfused within two hours to a small child with probable aplastic anemia.[26] Seventy-three per cent of these cells were reticulocytes. As a result of the transfusion the child's reticulocyte count was raised by 17 per cent.

The child's blood group was A₂MNRh+, and since the cells from patient M. G. belonged to group OMNRh+ it was possible to follow the survival of the latter by using B serum. The results of this experiment are presented and discussed in
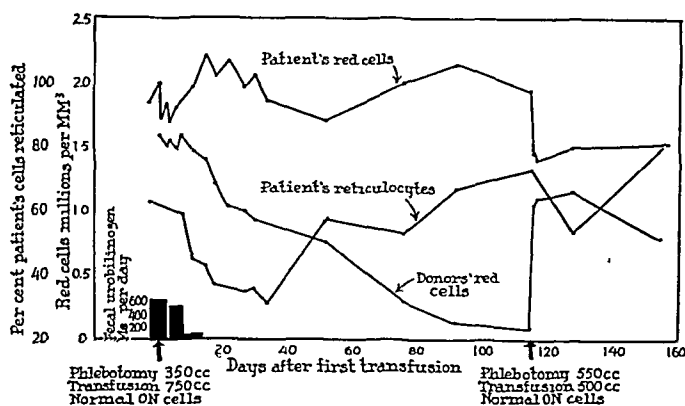
Chart 5 (case 2).—Hematologic changes during transfusion study.

detail in a separate paper.[2] It was found that the donated reticulocytes gradually matured in the child's circulation over a period of about six days and that all the transfused cells were destroyed in approximately eight days. It was demonstrated, however, that the reticulocytes were not destroyed until they had become mature. The child was later given two transfusions of normal cells, which were destroyed far more slowly.

Transfusion of Patient's Plasma to a Person Without Anemia: Within two hours after the 550 cc. of blood (containing 50 cc. of 5 per cent sodium citrate) was drawn from patient M. G. on October 5, 400 cc. plasma had been separated after centrifugation and frozen at — 35 C. The plasma was kept in the frozen state until October 18. At that time it was thawed at 37 C. and given intravenously to a man (blood group B) who was convalescing from cerebral thrombosis. The recipient's red blood cell count (average of four separate counts), hemoglobin content (average of two photoelectric determinations), hematocrit value (Wintrobe) and icterus index were checked daily for three days prior to the transfusion

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26. The cells removed from the patient at the time of the first phlebotomy were also transfused to a small child, but it was necessary to discontinue this experiment for technical reasons.

of plasma and at two and twenty-one hours and every two days for ten days thereafter. No significant changes were produced by transfusion of 400 cc. of plasma which had been removed from the patient with hemolytic anemia.

COMMENT

Present State of Ignorance Regarding Hemolytic Anemias.—The hemolytic anemias have been classified by many writers and the various causes repeatedly enumerated.[27] They remain, however, among the least understood of all diseases encountered in the study of medicine.

For the sake of simplicity, the hemolytic disorders might be divided into two large groups: (1) those that are due to "extrinsic" agents and (2) those that are either congenital or due to "intrinsic" causes. It should be borne in mind that certain extrinsic agents, such as the malaria parasite, may initiate activity of hemolytic mechanisms that are apparently similar to or identical with those operating in cases due to purely intrinsic causes.[28] Moreover, sharp division of the group due to intrinsic causes into those that are congenital and those that are acquired is difficult, as will be discussed subsequently. The exact mode of action of various extrinsic agents, such as bacteria, parasites and chemicals, is not understood. However, the group due to intrinsic causes is even more mysterious, and it is this group which will be referred to for the most part in the subsequent discussion.

Much of the controversy relating to the group of intrinsic disorders is centered about one question. Are the patient's cells in any given case destroyed rapidly because they themselves are defective or because they are acted on by an abnormal destructive mechanism? The abnormal hemolytic processes operating in persons with intrinsic hemolytic disorders are of many types, but all of them are believed to involve aberrations of the reticuloendothelial system, particularly the spleen. The respective roles of various hemolysins and agglutinins, presumably produced by the reticuloendothelial system and perhaps by lymphoid tissue, and of erythrostasis in the spleen have been discussed at length by Dameshek,[29] Ham and Castle [30] and others.[31]

27. (*a*) Pepper, O. H. P.: A Survey of the So-Called Hemolytic Anemias, Ann. Int. Med. **12**:796-810 (Dec.) 1938. (*b*) Haden, R. L.: The Nature of Hemolytic Anemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939. (*c*) Davis, L. J.: Haemolytic Anaemias, Edinburgh M. J. **50**:589-616, 1943. (*d*) Dameshek and Schwartz.[20] •

28. Foy, H.; Kondi, A.; Rebelo, A., and Soeiro, A.: Survival of Transfused Red Cells in Blackwater Fever Circulation and of Blackwater Red Cells in Normal Circulation, Tr. Roy. Soc. Trop. Med. & Hyg. **38**:271-286 (March) 1945.

29. Dameshek, W.: (*a*) Hemolytic Syndromes: A Five Year Progress Report, Bull. New England M. Center **5**:74-79 (April) 1943; (*b*) Medical Progress: Hematology, New England J. Med. **230**:514-521 (April 27); 542-550 (May 4)

Significance of Spherocytes.—The controversy just referred to involves particularly cases in which spherocytes are present. These cells were formerly regarded solely as products of defective erythropoiesis and were considered pathognomonic of congenital hemolytic jaundice. *The term "spherocytic jaundice" was therefore applied to this disease entity.*[32] More recently, however, these cells have been described in cases of hemolytic disorders labeled "acquired" or "atypical."[33] Moreover, spherocytosis and increased osmotic fragility have been observed in normal cells after exposure to agents such as hemolytic serums,[20] lysolecithin [31c] and heat.[34]

Dameshek [29c] has stated that he regards all spherocytes as cells which have been injured after delivery from the bone marrow. He postulates the injurious action of specific hemolysins not only in "acquired" hemolytic anemias but also in congenital hemolytic jaundice and in nocturnal hemoglobinuria. This view is held in spite of the fact that hemolysins have been demonstrated in vitro in only a few cases of the "acquired" and in no cases of the other types of hemolytic anemia —and in spite of the fact that circulating hemolysins have been demonstrated in the absence of spherocytes.[35]

1944; (c) Medical Progress: Hematology, ibid. **232**:250-255 (March 1); 280-286 (March 8) 1945.

30. Ham, T. H., and Castle, W. B.: Studies on Destruction of Red Blood Cells: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Proc. Am. Philos. Soc. **82**:411-419 (May 20) 1940; Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians **55**:127-132, 1940.

31. (a) Doan, C. A.; Wiseman, B. K., and Erf, L. A.: Studies in Hemolytic Jaundice, Ohio State M. J. **30**:493-504 (Aug. 1) 1934. (b) Sharpe, J. C., and Tollman, J. P.: Refractory Hemolytic Anemia: A Report of Five Cases in Which Treatment Was with Splenectomy, Arch. Int. Med. **70**:11-32 (July) 1942. (c) Dameshek, W., and Miller, E. B.: Pathogenetic Mechanisms in Hemolytic Anemias, ibid. **72**:1-17 (July) 1943. (d) Dameshek and Schwartz.[20]

32. Krumbhaar, E. B.: Modern Concepts of Anemia from the Clinical Standpoint, Bull. New York Acad. Med. **13**:501-511 (Sept.) 1937.

33. (a) Watson, C. J., and Clarke, W. O.: Hemolytic Anemia, Staff Meet., Bull. Hosp. Univ. Minnesota **12**:356-370 (April 4) 1941. (b) Mason, V. R.: Acquired Hemolytic Anemia, Arch. Int. Med. **72**:471-493 (Oct.) 1943. (c) Dameshek and Schwartz.[20] (d) Dameshek.[29]

34. Shen, S. C.; Ham, T. H., and Fleming, E. M.: Studies on Destruction of Red Blood Cells: III. Mechanism and Complications of Hemoglobinuria in Patients with Thermal Burns; Spherocytosis and Increased Osmotic Fragility of Red Blood Cells, New England J. Med. **229**:701-713 (Nov. 4) 1943.

35. Farrar, G. E., Jr.; Burnett, W. E., and Steigman, A. J.: Hemolysinic Anemia and Hepatic Degeneration Cured by Splenectomy, Am. J. M. Sc. **200**:164-172 (Aug.) 1940.

Reference has already been made to the studies of Dacie and Mollison,[4] who found that cells from a patient with congenital hemolytic jaundice, taken both before and after splenectomy, disappeared rapidly after transfusion into normal recipients. Normal cells, on the other hand, survived normally when transfused into patients with this disorder. These observations have been interpreted by Dacie and Mollison and by Davis [27c] as indicating that defective formation of erythrocytes is the basic abnormality in congenital hemolytic jaundice. Dameshek,[29b] however, stated that these experiments do not exclude the role of hemolysins because "spherocytes, already being . . . on the road to hemolysis, are more quickly destroyed in the intact spleen" of a normal recipient. Dacie and Mollison admitted the possibility that the hemolytic agent postulated by Dameshek (although not demonstrated in vitro) might be specific for the patient's own cells and would thus permit normal donated cells to survive normally.

In cases of congenital hemolytic jaundice there is obvious need of more transfusion experiments of the type reported by Dacie and Mollison. It is also essential that these studies be accompanied by careful search for autohemolysins and isohemolysins. This need is more urgent in view of the fact that some investigators [36] have described cases of congenital hemolytic jaundice in which transfused normal cells may have been destroyed rapidly.

Differentiation of Congenital and Acquired or Atypical Hemolytic Jaundice.—Diagnosis is relatively easy in cases of typical congenital hemolytic jaundice. However, differentiation from the heterogeneous group of cases of "acquired" or atypical hemolytic jaundice may often be very difficult, as pointed out by numerous observers.[37] The late Lord Dawson of Penn [36a] expressed the opinion that the "defects themselves are inborn," and he doubted the existence of acquired forms of hemolytic anemia. Doan and associates [31a] likewise expressed the belief that "hemolytic icterus is a disease, usually, if not always, congenital." On

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36. (*a*) Dawson, B. E.: The Hume Lectures on Haemolytic Icterus, Brit. M. J. **1**:921-928 (May 30) 1931: (*b*) Lowe, R. C.: A Study of Hemoglobin Metabolism and Hematology in a Case of Congenital Hemolytic Jaundice During Clinical Crisis, Repeated Transfusions and Before and After Splenectomy, Am. J. M. Sc. **206**:347-352 (Sept.) 1943.

37. (*a*) Davidson, L. S. P.: Macrocytic Haemolytic Anaemia, Quart. J. Med. **25**:543-578 (Oct.) 1932. (*b*) Josephs, H. W.: Studies in Haemolytic Anemia: I. Haemolysis, Compensatory Regeneration and Erythroblastosis, Bull. Johns Hopkins Hosp. **62**:25-52 (Jan.) 1938. (*c*) Rastetter, J. W., and Murphy, F. D.: Acquired Hemolytic Jaundice, Am. J. Digest. Dis. & Nutrition **4**:805-810 (Feb.) 1938. (*d*) Sutton, H. B., and Moore, N. S.: The Diagnosis and Treatment of Congenital Hemolytic (Spherocytic) Jaundice: Report of a Case with Unusual Blood Findings Altered by Liver Therapy, Ann. Int. Med. **21**:698-708 (Oct.) 1944. (*e*) Davis.[27c] (*f*) Doan, Wiseman and Erf.[31a] (*g*) Mason.[33b]

the contrary, Dameshek [29b] has more recently stated that most hemolytic anemias are not hereditary. Davis,[27c] in 1943, reviewed a group of 47 cases of subacute and chronic idiopathic hemolytic anemia and concluded that most of these cases differed fundamentally from congenital hemolytic jaundice. Microspherocytosis with increased osmotic fragility of the red cells was recorded in only 4 of the 47 cases. The response to splenectomy was variable in contrast to the uniformly favorable results in cases of the more familiar disorder.

Thompson [38] has studied three family groups in which hemolytic anemia was present in various generations but in which spherocytes (and leptocytes) were lacking. Because of this report and because of ignorance concerning the nature of acquired hemolytic anemias it is probably wise to apply the term "atypical" to this heterogeneous group as suggested by Thompson. Accordingly, both cases described in this paper have been labeled "atypical" rather than "acquired."

Use of Transfusions in the Study of Hemolytic Anemias.—Of Intrinsic Origin: It is clear that present knowledge of the hemolytic disorders is decidedly limited. Even in the case of congenital hemolytic jaundice, which is perhaps the best known of the hemolytic diseases, there are many questions which remain unanswered. The atypical cases are the subject of even more debate and speculation. Much of the difficulty encountered in studying the hemolytic anemias can be attributed to the fact that in vivo processes often cannot be duplicated in the test tube. It is therefore logical that attention should be directed to the usefulness of transfusion experiments, which are the only means available for studying in vivo the fate of certain cells.

In case 1 of the present report there was no opportunity to determine the manner of disappearance of the patient's cells after transfusion into a normal recipient. However, normal cells were rapidly destroyed in the patient's circulation, and it is considered likely that their destruction was initiated by cold agglutinins (and possibly a_1 agglutinins) of high thermal amplitude. In accordance with the views of Stats and Wasserman [22] and Dameshek,[29c] it is suggested that a small degree of intravascular agglutination of both autologous and donated cells rendered the erythrocytes highly susceptible to destruction. Complete destruction of the agglutinated cells may have been brought about by the mechanical trauma of circulation or by more specific activity of the reticuloendothelial system or by both. The fact that rapid destruction of cells continued for some time after splenectomy suggests that the spleen may not have been responsible. Neither autohemolysins nor isohemolysins could be

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38. Thompson, W. P.: Hemolytic Jaundice, Bull. New York Acad. Med. **15:** 177-187 (March) 1939.

demonstrated, but it is possible that their presence was masked by the irregular agglutinins [20] or by some type of blocking antibody.[39]

At any rate, it is fair to suspect that in this case the fundamental abnormality was not in the process of red cell formation but rather in the mechanism of red cell destruction. Anatomically speaking, it was primarily not in the erythron but in the reticuloendothelial system—that is, the tissue responsible for production of irregular agglutinins and for the breakdown (particularly in the spleen) of both normal and agglutinated or damaged cells.

In case 2 the patient's cells were rapidly destroyed in her own body and after transfusion to a child who destroyed normal cells at a much slower rate. Normal cells donated to this patient disappeared slowly in a linear fashion. Moreover, 400 cc. of the patient's plasma, which contained no irregular antibodies demonstrable in vitro, did not have a measurable hemolytic effect on the cells of a normal recipient. It seems likely, therefore, that the fundamental defect in this case was in the erythron, that is, the erythroid cells of the bone marrow and the erythrocytes themselves.

Some authorities might argue that in the second case the red cells were not defective "at birth" but were damaged "postnatally" by hemolysins after, delivery from the marrow. They would argue further that hemolysins were present even though they could not be demonstrated in vitro. They would contend still further that the hemolysins were specific for the patient's own cells and therefore allowed normal donated cells to be destroyed slowly by normal processes. There is little to be gained by dogmatically denying the existence of such hemolysins. However, it seems fair to state that the burden of proof rests on the authors who assert that they do exist and that they are largely responsible for the rapid and indiscriminate destruction of erythrocytes in most of the intrinsic cases, both congenital and atypical. Before this controversy can be settled, much more must be learned concerning the exact manner and site of formation of antibodies,[40] the role of lymphocytes in this process [41] and the nature of blocking antibodies.[39]

39. Wiener, A. S.: A New Test (Blocking Test) for Rh Sensitization, Proc. Soc. Exper. Biol. & Med. **56**:173-176 (June) 1944. Fisk, R. T., and Morrow, P.: The Occurrence of Anti-Rh Blocking Antibodies in Anti-Rh Serums, ibid. **58**: 72-73 (Jan.) 1945. Diamond, L. K., and Abelson, N. M.: The Demonstration of Anti-Rh Agglutinins: An Accurate and Rapid Slide Test, J. Lab. & Clin. Med. **30**:204-212 (March) 1945. Levine, P., and Gilmore, E. L.: The First Stage of Antigen-Antibody Reaction in Infectious Mononucleosis, Science **101**:411-412 (April 20) 1945.

40. Burnet, F. F.; Freeman, M.; Jackson, A. V., and Bush, D.: The Production of Antibodies, Melbourne, Australia, Macmillan & Co., Ltd., 1941.

41. Kass, E. H.: The Occurrence of Normal-Serum Gamma-Globulin in Human Lymphocytes, Science **101**:337-338 (March 30) 1945.

Transfusion experiments of the type described deserve much wider use in the study of hemolytic anemias. More extensive application of this in vivo test will provide valuable information concerning its usefulness and limitations. It would be of interest to transfuse into normal recipients (or into patients with anemia due to loss of blood) erythrocytes from patients with sickle cell anemia, sickle cell trait and target cell–oval cell syndromes. Additional experiments with cells from patients with nocturnal hemoglobinuria will also be worth while. In cases of chronic hemolytic anemia of only moderate severity, it is considered safe to remove several hundred cubic centimeters of the patient's blood, provided the phlebotomy is followed immediately by a transfusion of normal whole blood or red cells. In fact, patients may benefit temporarily from this procedure, inasmuch as they receive normal cells in exchange for defective cells.

Transfusion of normal erythrocytes into patients with almost any type of hemolytic anemia, either extrinsic or intrinsic in type, would yield information of value provided the pattern of disappearance of the cells can be determined by means of differential agglutination tests. Observations on the effect of transfusion of serum or plasma from patients with hemolytic disorders into normal recipients would also be of interest. It is believed, however, that the latter type of experiment will seldom be justified in view of the possible risk to the recipient. In any case, certain possibilities must be kept in mind in interpreting the results of such experiments, namely (1) specificity of hemolysins for the patient's own cells, (2) complete binding of hemolysins by the patient's cells so that none may be present in separated plasma and (3) absorption of transfused hemolysins by the recipient's erythrocytes or tissue cells or both in such a way that hemolysis does not occur. In addition, the quantity of plasma transfused must obviously be taken into account.

It is reasonable at this point to speculate on the manner in which transfusion experiments might aid in classifying the various hemolytic diseases. On the basis of such experiments, it might be possible to divide intrinsic hemolytic anemias into two large groups, as shown in table 3.

It must be emphasized that this classification is largely conjectural, and much more work will be necessary before it can have meaning. Furthermore, it is likely that the division into groups A and B will not be clearcut—that is, it may be found that patients in group A destroy normal donated cells rapidly during acute phases of their illness. Some of the studies already reported suggest that this may be the case. It may also be found that cells taken from patients in group B, once they have been damaged or in some way acted on by agglutinins or hemol-

ysins, are rapidly destroyed after transfusion into normal recipients. It is believed, however, that in spite of obvious limitations transfusion experiments will be of distinct value in exploring the intrinsic hemolytic anemias. They might also throw light on the mechanisms involved in some of the cases of hemolytic anemia of extrinsic origin, caused by burns, chemicals and infectious agents.

Of Extrinsic Origin: The value of this type of study in investigation of the extrinsic group is shown by the recent report of Foy and associates.[28] It was found that cells from a patient with active blackwater fever

TABLE 3.—*Conjectural Classification of Intrinsic Hemolytic Anemias on the Basis of Transfusion Experiments*

Group	Manner of Destruction of Patient's Cells After Transfusion into Normal Recipient	Manner of Destruction of Normal Donated Cells After Transfusion into Patient	Effect of Patient's Serum or Plasma on Cells of Normal Recipient	Suspected Site of Hemolytic Abnormality	Clinical Diagnoses
A	Rapid, at least partially exponential	Normal, linear (or variable during acute phases ?)	Probably little or none	Erythron	Congenital hemolytic jaundice; sickle cell anemia; thalassemia; nocturnal hemoglobinuria; certain chronic atypical forms (such as case 2)
B	No experiments on which to base opinion	Rapid, chiefly exponential	No experiments on which to base opinion	Reticuloendothelial system (including spleen) and its products (antibodies)	Acute atypical hemolytic anemia; certain chronic atypical forms (such as case 1); some cases associated with malignant growths, *disseminated lupus erythematosus*, etc.; cold hemoglobinuria (syphilitic); hemolytic disease of newborn *

* Hemolytic disease of the newborn, or erythroblastosis fetalis, is included here for the sake of completeness. It differs from the other hemolytic disorders listed in that antibodies are formed in the mother and passively transferred to the child.

survived only six days after transfusion into a normal recipient. The survival time of normal cells transfused into patients with blackwater fever nine days after active hemolysis had ceased was thirty to thirty-five days. Eighteen months later the survival time of donated cells was normal. According to the authors, these results indicated the presence of a factor capable of destroying all cells and once cells of persons with blackwater fever were acted on by this factor they were readily destroyed even in a normal circulation. It was found, however, that 500 cc. of plasma from a patient with active blackwater fever transfused into a patient with an acute attack of malaria failed to cause hemolysis in the recipient. It was concluded that either insufficient plasma was used in this experiment or any hemolysins present had been "used up" by the blackwater cells.

This interesting report from Foy's laboratory serves to illustrate three important points: (1) that transfusion experiments are useful in studying hemolytic anemia of extrinsic origin; (2) that extrinsic factors may initiate the activity of mechanisms similar to, or identical with, those operating in purely intrinsic cases and (3) that cells, other than spherocytes, which have been damaged by hemolysins are rapidly destroyed, even in a normal circulation. If it is found that these results apply to some of the anemias of purely intrinsic origin and if the cells of some of the patients with intrinsic hemolytic anemias of group B are found to be destroyed normally in normal circulations, it will be necessary to add a group C to the classification shown in table 3. Included in group C would be the diseases of patients whose cells are rapidly destroyed in normal circulations and who themselves destroy normal cells rapidly.

Cold Hemagglutinins in Hemolytic Anemia: Since Widal's [42] initial observations in 1908, the presence of cold hemagglutinins in the serum of patients with hemolytic anemia has been noted by many observers,[43] but in only 3 previously reported cases has activity of these antibodies been demonstrable at body temperature.[44] As a general rule, the thermal amplitude of cold agglutinins is proportional to the titer,[22] activity at body temperature being expected only when the titer is extremely high at temperatures near 0 C. Case 1, in which the titer at 4 C. was not

42. Widal, F.; Abrami, P., and Brulé, M.: Autoagglutination des hématies dans l'ictère hémolytique acquis, Compt. rend. Soc. de biol. **64**:655-657, 1908.

43. (*a*) Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia: Certain Observations in a Series of Thirty-Five Cases, Ann. Int. Med. **12**:1782-1796 (May) 1939. (*b*) Antopol, W.; Applebaum, I., and Goldman, L.: Two Cases of Acute Hemolytic Anemia with Auto-Agglutination Following Sulfanilamide Therapy, J. A. M. A. **113**:488-489 (Aug. 5) 1939. (*c*) Reisner, E. H., and Kalkstein, M.: Auto-Hemolysinic Anemia with Autoagglutination: Improvement After Splenectomy, Am. J. M. Sc. **203**:313-322 (March) 1942. (*d*) Rothstein, I., and Cohn, S.: Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy, Ann. Int. Med. **16**:152-162 (Jan.) 1942. (*e*) Dameshek, W.: Cold Agglutinins in Acute Hemolytic Reactions, J. A. M. A. **123**:77-80 (Sept. 11) 1943. (*f*) Layne, J. A., and Schemm, F. R.: Acute Macrocytic Hemolytic Anemia Occurring Following Administration of Sulfadiazine, J. Lab. & Clin. Med. **29**:347-351 (April) 1944. (*g*) Köpplin, F.: Autohämagglutination und Anämie, Ztschr. f. klin. Med. **130**:784-788, 1936. (*h*) Dameshek.[13] (*i*) Dameshek and Schwartz.[20] (*j*) Mason.[33b]

44. (*a*) Wiener, A. S.: Hemolytic Transfusion Reactions: I. Diagnosis, with Special Reference to the Method of Differential Agglutination, Am. J. Clin. Path. **12**:189-199 (April) 1942. (*b*) Kracke, R. R., and Hoffman, B. J.: Chronic Hemolytic Anemia with Autoagglutination and Hyperglobulinemia: Report of a Fatal Case, Ann. Int. Med. **19**:673-684 (Oct.) 1943. (*c*) Evans, R. S.: Acute Hemolytic Anemia with Autoagglutination: A Case Report, Stanford M. Bull. **1**:178-182 (Aug.) 1943.

remarkable, is therefore one of the few notable exceptions to this general rule and serves to emphasize that' thermal amplitude may be a "constitutional characteristic." [22]

Widal and associates [42] expressed the opinion that cold agglutinins might serve to distinguish acquired hemolytic anemia from the congenital type, but it has since been found that these agglutinins are present in significant titer in relatively few cases.[45] Moreover, they have been described by Masters and associates [46] and by Young [21] in cases that conformed in every respect to the congenital type.

The role of cold hemagglutinins in the process of rapid destruction of erythrocytes has been the subject of considerable debate. In some instances the cold agglutinins have persisted in undiminished titer after the hemolytic process has subsided and even after splenectomy, as in case 1 of this report. In addition, it has been emphasized that hemolytic anemias have been described which were identical in every respect except for the presence of cold agglutinins in some and the absence of same in others. After summarizing the available evidence, Stats and Wasserman [22] concluded that these antibodies were the result rather than the cause of hemolytic anemia.

Wiener,[44a] on the contrary, after describing a case in which autoagglutinins were active at body temperature, expressed the opinion that they had played a part in the destruction of the patient's erythrocytes in vivo. This conclusion appears reasonable so far as it applies to cases in which the agglutinins have extremely high thermal amplitude. However, complete understanding of the role of cold hemagglutinins in hemolytic disorders must await further observation, with particular emphasis on the mechanical fragility of weakly agglutinated erythrocytes.

The relation of cold agglutinins to splenomegaly and their disappearance following splenectomy in some cases and persistence in others have been discussed elsewhere.[21]

Multiple Evidence of Abnormal Antibody Production: It was pointed out in a separate paper [1] that in 3 of the 5 reported cases of development of a_1 or a_2 agglutinins following transfusion the patients were suffering from atypical hemolytic anemia. It was further emphasized that in 2 of these cases, other irregular antibodies were present in addition to the a_1 and a_2 antibodies. Kracke and Hoffman [44b] have recently described a case of chronic atypical hemolytic anemia in which the patient's serum contained (1) autoagglutinins active at body temperature, (2) antibodies producing positive reactions to Wassermann,

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45. Stats and Wasserman.[22] Watson.[43a]

46. Masters, J. M.; Zerfas, L. G., and Mettel, H. B.: Congenital Hemolytic Icterus: Treatment with Splenectomy; Reports of Two Cases, Am. J. Dis. Child. **37**:1254-1259 (June) 1929.

Kahn, Kline and Eagle tests on repeated occasions and (3) globulin in a concentration of 5.36 Gm. per hundred cubic centimeters. The serologic reactions for syphilis became negative within two weeks after splenectomy.

All these observations point to abnormal activity of the reticuloendothelial system as a common denominator in certain persons in whom atypical hemolytic anemia is liable to develop. It appears as though this remarkable tissue (and perhaps the lymphoid tissue[41]) for no apparent reason sometimes produces sports of various types and that only one of the various sports produced may be responsible for rapid destruction of red cells. Whether or not this phenomenal activity is dependent on a fundamental constitutional abnormality is not clear.

Inhibitory Properties of Serum: In case 1 it was repeatedly observed that cold hemagglutinins had greater thermal amplitude after being separated in saline eludates from the whole serum. This fact indicated that the serum had an inhibitory property, the exact nature of which could not be determined because of several practical difficulties.

Josephs[47] demonstrated in normal human plasma a substance which reduced the rate of blood destruction in sickle cell anemia and in congenital hemolytic jaundice. It was suggested that the function of this substance was to aid in maintaining the normal equilibrium between formation and destruction of erythrocytes and that a lack of this substance might be responsible for certain hemolytic phenomena.

Maegraith, Findlay and Martin[48] found that washed tissues (lung, liver, kidney, spleen, bone marrow and muscle) lysed saline suspensions of red cells of the same species (man, monkey and guinea pig). Lysis was inhibited by addition of serum to the tissue–red cell mixture. The lytic agent, which was thought to be an enzyme, appeared to be species specific, while the serum inhibitor was not. These investigators postulated that the degree of hemolysis occurring at any time in a given animal might depend on the balance of inhibitor over lytic enzyme activity. They further suggested that some hemolytic disorders might be due either to interference with the activity of the inhibitor or to its actual destruction.

Farrar, Burnett and Steigman[35] demonstrated the presence of a hemolysin in a case of atypical hemolytic anemia and found that it was neutralized by normal homologous serum. Ecker, Castro and Seifter[49]

47. Josephs, H. W.: Studies in Haemolytic Anemia: II. The Presence of an Anti-Haemolytic Factor in Human Plasma, Bull. Johns Hopkins Hosp. **62**:53-69 (Jan.) 1938.

48. Maegraith, B.; Findlay, G. M., and Martin, N. H.: Mechanism of Lysis of Red Blood Cells, Nature, London **151**:252 (Feb. 27) 1943.

isolated from human serum a protein fraction which inhibited certain serologic reactions. Whether or not this substance is related to or identical with the inhibitory substances referred to by other investigators remains to be seen. It is clear, however, that the possible function of serum inhibitors in maintaining the erythrocyte formation-destruction balance cannot be overlooked. Moreover, it may be found that some hemolytic disorders, particularly those of group B, are due to the absence or inactivation of inhibitors rather than to the presence of irregular hemolysins or agglutinins.

The beneficial effect of transfusions in hemolytic anemia has been noted by many observers. A single transfusion has sometimes been apparently curative or has at least resulted in improvement beyond that attributable to the quantity of red cells given.[20] Beard [50] has recently emphasized the value of plasma transfusions and has reported uniformly good results from daily administration of large quantities. In view of the probable existence of inhibitory substances in plasma and the high incidence of reactions following transfusions of whole blood, the rationale of plasma therapy in hemolytic anemia is evident.

Value of Splenectomy: The wisdom of performing splenectomy in cases of congenital hemolytic jaundice has long been established. The results of this operation in atypical cases, however, have been highly irregular.[51] One cannot be certain that splenectomy alone was responsible for the apparent cure in case 1 of this report, nor can one predict what might be accomplished by this procedure in case 2. In cases of acute illness there is relatively little time for detailed studies, but in the cases of the more chronic types it is obviously desirable to make extensive investigations prior to and following operation. Information accumulated in this way may make it possible for the physician in the future more judiciously to select certain atypical cases for splenectomy.

Initiation of Hemolytic Activity: The nature of the stimulus which initiates rapid destruction of erythrocytes in intrinsic cases is not understood. Numerous hypotheses have been offered, but none is entirely satisfactory. Does the patient suddenly become sensitized to his own erythrocytes and thus develop autoagglutinins or autohemolysins [52]? Is there destruction, inactivation or deficiency of inhibitory substances which ordinarily hold lytic factors in balance [53]? Does the phagocytic

49. Ecker, E. E.; Castro, G. L., and Seifter, S.: Isolation from Fresh Human Serum of a Fraction Which Inhibits Certain Serological Reactions, Proc. Soc. Exper. Biol. & Med. **58**:95-96 (Jan.) 1945.

50. Beard, M. F.: Hemolytic Anemia, South. M. J. **37**:448-450 (Aug.) 1944.

51. Lawrence, J. S.: Indications for Splenectomy in a Medical Practice, Internat. Clin. **2**:221-238 (June) 1937. Dameshek.[13] Davis.[27c] Thompson.[38]

52. Wiener, A. S.: Macrocytic Anemia of Pregnancy, J. A. M. A. **125**:990 (Aug. 5) 1944. Dameshek and Schwartz.[20] Dameshek.[29c]

53. Masters, Zerfas and Mettel.[46] Josephs.[47]

activity of the spleen and other parts of the reticuloendothelial system suddenly get out of hand—and if so, why? These and many other questions remain unanswered. The patient who at age 1 or age 60 suddenly or gradually begins to destroy his own cells at a rapid rate furnishes food for speculation. Reflection on this puzzle makes one appreciate that even the normal mechanism of red cell destruction is not understood.

The observations recorded in this paper represent an attempt to clarify the factors operating in 2 unusual examples of hemolytic disease. They do not, however, provide a solution of even one of the many problems presented by this mysterious group of disorders. Further struggle with these problems is needed, and it can be expected to produce valuable results because "the disease hemolytic anemia has an interest beyond itself." [36a]

SUMMARY

Clinical and laboratory observations on 2 cases of chronic atypical hemolytic anemia are presented in detail.

The important features of case 1 were (*a*) rapid destruction of all transfused red cells received from 30 donors, (*b*) presence of cold hemagglutinins which became slightly active at body temperature, (*c*) development of a_1 agglutinins following twenty-one transfusions of A_1 blood, and (*d*) apparent cure following splenectomy in spite of the persistence of cold hemagglutinins.

In case 2 phlebotomy was performed twice and followed immediately, each time, by transfusion of normal erythrocytes. The patient's red cells were rapidly destroyed after transfusion to a small child, but the patient's plasma had no hemolytic effect on the cells of a normal recipient. Donated normal cells survived normally in the patient's circulation.

The usefulness of transfusion experiments in the study of hemolytic anemias is emphasized. It is suggested that on the basis of such experiments it may be possible to divide the intrinsic hemolytic disorders into 2 groups: A, in which the primary defect is in the red cell itself, and B, in which the primary abnormality is in the hemolytic mechanism.

The behavior of cold hemagglutinins and a_1 agglutinins in case 1 is described. In view of the high thermal amplitude of these antibodies, their role in blood destruction cannot be minimized.

The significance of an inhibitory substance in the serum of case 1 and in normal serum or plasma is discussed in relation to the rationale of plasma therapy in hemolytic anemia.

ABSORPTION, DISTRIBUTION AND EXCRETION OF STREPTOMYCIN

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STREPTOMYCIN, an antibiotic substance obtained from the micro-organism Actinomyces griseus, was described in January 1944 by Schatz, Bugie and Waksman.[1] This material was shown to possess activity in vitro over a wide range of bacteria but was of particular interest because it was effective against many bacteria which were not susceptible to the chemotherapeutic substances then available for the treatment of human infections. Subsequent reports have confirmed these observations and, in addition, have shown that streptomycin is effective in the treatment of experimental infections with organisms of the Eberthella and Salmonella groups [2] and with Pseudomonas aeruginosa, Shigella gallinarum, Brucella abortus and Proteus vulgaris,[3] as well as with Pasteurella tularensis [4] and with the Klebsiella organisms.[5] Streptomycin was also found to possess activity against the tubercle bacillus both in vitro [6] and in vivo.[7] The toxicity of a partially purified product for mice was reported to be of a fairly low order.[2]

1. Schatz, A.; Bugie, E., and Waksman, S. A.: Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria, Proc. Soc. Exper. Biol. & Med. **55**:66, 1944.

2. Robinson, H. J.; Smith, D. G., and Graessle, O. E.: Chemotherapeutic Properties of Streptomycin, Proc. Soc. Exper. Biol. & Med. **57**:226, 1944.

3. Jones, D.; Metzger, H. J.; Schatz, A., and Waksman, S. A.: Control of Gram-Negative Bacteria in·Experimental Animals by Streptomycin, Science **100**:103, 1944.

4. Heilman, F. R.: Streptomycin in the Treatment of Experimental Tularemia, Proc. Staff Meet., Mayo Clin. **19**:553, 1944.

5. Heilman, F. R.: Streptomycin in the Treatment of Experimental Infections with Micro-Organisms of the Friedländer Group (Klebsiella), Proc. Staff Meet., Mayo Clin. **20**:33, 1945.

As is the case with penicillin, streptomycin is at present measured by reference to its antibiotic activity. The unit of streptomycin has been defined as that amount of the material which completely inhibits the growth of a strain of Escherichia coli in 1 cc. of nutrient broth. Recently a method has been described for the preparation of crystalline streptomycin hydrochloride,[8] which is reported to have an activity of 800 units per milligram. The present unit would then be equivalent to 0.00125 mg. of the crystalline material.[8a]

Within the past year streptomycin has become available in sufficient quantity for limited trial against human infections. One report has appeared regarding its use in typhoid,[9] and in this report the toxicity of the material was considered to be compatible with clinical use.

The present studies were undertaken to determine the absorption, distribution and excretion of streptomycin when given by various routes and to provide an understanding of the problems of administration of the drug.

METHODS AND MATERIALS

The concentration of streptomycin in various body fluids was determined by a method recently described by Stebbins and Robinson,[10] with minor modifications. The technic of this test is as follows: The test organism, known as Staphylococcus aureus S. M.,[11] is grown in nutrient broth for sixteen hours at 37 C. A 10^{-4} dilution of this culture is made into the melted test agar [12] at a temperature of 45 C. After thorough mixing, the test agar is pipetted into sterile Petri dishes in 10 cc. quantities and allowed to solidify. Beveled porcelain cylinders are heated, and the beveled end is placed on the surface of the agar, forming a seal between the cylinder and the agar as cooling occurs. The cylinders are then

6. Schatz, A., and Waksman, S. A.: Effect of Streptomycin and Other Antibiotic Substances upon Mycobacterium Tuberculosis and Related Organisms, Proc. Soc. Exper. Biol. & Med. **57**:244, 1944.

7. Feldman, W. H., and Hinshaw, H. C.: Effects of Streptomycin on Experimental Tuberculosis in Guinea Pigs: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **19**:593, 1944.

8. Kuehl, F. A.; Peck, R. L.; Walti, A., and Falkers, K.: Streptomyces Antibiotics: I. Crystalline Salts of Streptomycin and Streptothricin, Science **102**: 34, 1945.

8a. Shortly after the preparation of this manuscript it was proposed that amounts of streptomycin be expressed as equivalents of streptomycin base. Under this plan 1 unit represents 1 microgram of pure streptomycin base and 1,000,000 units represents 1 Gm. It is expected that this plan will be generally adopted.

9. Reimann, H. A.; Elias, W. F., and Price, A. H.: Streptomycin for Typhoid: A Pharmacologic Study, J. A. M. A. **128**:175 (May 19) 1945.

10. Stebbins, R. B., and Robinson, H. J.: A Method for Determination of Streptomycin in Body Fluids, Proc. Soc. Exper. Biol. & Med. **59**:255, 1945.

11. Obtained from the Merck Institute for Therapeutic Research.

12. Bacto peptone 1 per cent, Bacto beef extract 0.4 per cent, salt 0.25 per cent, agar 1.5 per cent. The p_H is adjusted to 7.5 with sodium hydroxide.

filled with fluids containing streptomycin and the Petri dishes incubated for sixteen to eighteen hours at 30 C. Well defined zones of inhibition of growth are then apparent around the cylinders. The diameters of these zones are proportional to the concentration of streptomycin in the specimen and are measured to the nearest 0.5 mm. To minimize the error, each specimen is run in triplicate, different Petri dishes being used and the diameters of the three zones of inhibition averaged.

To determine the concentration of streptomycin in unknown specimens, it is · necessary to construct a standard curve of reference for each day's determinations. In the case of serum, this is accomplished by adding streptomycin to pooled normal serum in concentrations of 1, 2, 4, 8, 12, 16 and 20 units per cubic centimeter and handling the individual specimens as described previously. The diameters of the zones of inhibition are plotted against the known concentrations of strepto-

TABLE 1.—*Results of Assays Run on Normal Serum to Which Streptomycin Had Been Added*

Amount of Streptomycin Added to Normal Serum, Units per Cc.	Results of Assays, Units per Cc.					
	1	2	3	4	5	6
40	42.0	37.5	40.0	37.5	50.0	48.7
30	33.0	33.0	27.0	27.5	32.5	31.2
22	19.0	18.7	26.2			
14	14.0	11.2	13.0	13.5	10.5	14.1
6	6.2	5.8	5.5			

TABLE 2.—*Results of Assays Run on Normal Urine to Which Streptomycin Had Been Added*

Amount of Streptomycin Added to Normal Urine, Units per Cc.	Results of Assays, Units per Cc.					
	1	2	3	4	5	6
2,000	2,100	1,740	1,700	1,420	2,000	
1,000	1,000	1,070	850	940	1,000	1,000
500	475	500	500	495	550	
100	86	120	95	95	110	90
50	43	52.5	43.5	60		
10	8	8.5				

mycin. The concentration of streptomycin in the unknown serum may then be computed by reference to this curve. Unknown serums are diluted with pooled normal serums when necessary to insure a reading which will fall within the limits of the standard curve. The concentrations in pleural and abdominal fluids, spinal fluids and bile have likewise been determined by reference to this curve. In determining the concentration of streptomycin in urine, the most consistent results have been obtained by substituting tenth-molar phosphate buffer solution at p_H 7.4 for serum in making up the standard curve and by diluting the unknown urine with this buffer.

In order to determine the reliability of this method, streptomycin was added to pooled normal serum in various concentrations, and assays were run on each specimen on several occasions. The results are shown in table 1. In table 2 are shown the results of similar experiments when streptomycin was added to normal urine in amounts covering the usual range encountered in patients receiving the material. An analysis of these rather small samples shows that for serum the mean percentage error is + 0.43 ± 2.9 per cent (standard deviation 11.22)

TABLE 3.—*Data on Absorption, Distribution and Excretion of Streptomycin*
Twenty-five experiments on twenty-one subjects

No.	Sex	Age	Subject Weight, Lb.	Diagnosis	Streptomycin Dose, Units	Route	Serum Time† Hr.	Serum Time† Min.	Serum Units per Cc.	Urine Time, Hr.	Volume, Cc.	Units per Cc.	Units Excreted	% of Dose Excreted, Cumulative	Other Body Fluids Hr.	Units per Cc.
1	M	15	119	Urinary tract infection	50,000	Intravenously	:	5	6.5	1	125	55	6,875	13		
							:	15	6.5	2	200	27.5	5,500	24		
							:	30	3.75	3	64	12	648	26		
							1	:	2.5	4	127	16	2,032	30		
							2	:	1.7	6	160	13	1,020	34		
							3	:	1.5							
							4	:	1.2							
							6	:	Trace							
2	F	20	119	Pulmonary tuberculosis	100,000	Intravenously	:	4	16.0	2	158	325	51,350	51		
							:	30	10.0	4	90	140	12,600	64		
							1	:	7.2	10	300	40	12,000	75		
							1	30	4.5							
							2	:	3.3							
							3	:	2.7							
							4	:	2.3							
							8	:	1.0							
							10	:	Trace							
3	M	21	210	Pulmonary tuberculosis	200,000	Intravenously	:	5	20.0	2	400	162.5	65,000	32		
							:	30	14.0	4	177	200	35,400	50		
							1	:	9.0	12	1,165	32	37,280	68		
							1	30	7.0	24	400	32	12,800	75		
							2	:	6.0							
							4	:	3.8							
							8	:	2.0							
							10	:	1.2							
							12	:	1.0							
4	M	24	171	Pulmonary tuberculosis	200,000	Intravenously	:	9	25.0	2	900	87.5	78,750	39		
							:	30	15.0	4	850	37.5	31,875	55		
							1	:	8.7	12	1,405	25	35,125	72		
							1	30	7.5	24	300	Trace				
							2	:	7.0							
							4	:	3.5							
							8	:	1.7							
							10	:	Trace							

† Times are from the end of administration of streptomycin.

No.	Sex			Diagnosis	Dose	Route	Hr.			Hr.				
5	M	25	168	Normal subject	500,000	Intravenously	:	5	52.5	2	220	600	132,000	26
							:	30	41.0	6	215	425	91,375	44
							1	:30	25.5	12	270	300	81,000	61
							1	30	21.0					
							2		13.0					
							3		10.5					
							4		7.0					
							8		3.5					
							10		2.2					
							12		1.5					
6	M	54	143	Pulmonary tuberculosis	200,000	Subcutaneously	:	30	10.5	2	138	125	17,250	8
							1		10.0	4	163	235	39,480	28
							2		8.0	12	285	95	27,075	41
							4		4.5	24	333	50	16,600	50
							8		2.2					
							10		1.4					
							12		1.1					
7	M	61	162	Tuberculous adenitis	200,000	Subcutaneously	:	30	7.0	2	300	252	75,600	37
							1	:30	7.0	4	122	207	25,254	50
							1	30	8.0	12	311	95	29,830	65
							2		7.5	24	400	35	14,000	72
							4		4.0					
							8		1.7					
							10		1.5					
							12		1.0					
7	M	61	162	Tuberculous adenitis	200,000	Subcutaneously	:	30	6.3	2	170	215	36,550	18
							1	:30	8.0	4	200	185	37,000	36
							1	30	8.5	12	610	60	36,600	55
							2		8.0	22½	550	33	18,150	64
							4		5.7					
							8		2.0					
							10		1.5					
							12		1.0					
8	F	21	107	Pulmonary tuberculosis	100,000	Intramuscularly	:	30	5.5	2	245	100	24,500	24
							1	:30	6.0	4	225	60	13,500	38
							1	30	5.5	10	600	43	25,800	63
							2		5.5	24	345	9.4	3,243	67
							3		4.5					
							4		3.0					
							8		1.0					
							10		Trace					
9	F	25	99	Pulmonary tuberculosis	100,000	Intramuscularly	1		5.7	24	670	125	83,750	83
							2		3.5					
							6		1.25					
							10		Trace					

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TABLE 3.—Data on Absorption, Distribution and Excretion of Streptomycin—(Continued)

No.	Sex	Age	Weight, Lb.	Diagnosis	Dose, Units	Route	Serum Time Hr.	Serum Time Min.	Serum Units per Cc.	Urine Time, Hr.	Urine Volume, Cc.	Urine Units per Cc.	Urine Units Excreted	% of Dose Excreted, Cumulative	Other Body Fluids Hr.	Other Body Fluids Units per Cc.
10	M	25	156	Pulmonary tuberculosis	200,000	Intramuscularly	:	:30	10.0	2	775	75	57,125	28		
							1	::	11.0	4	440	43	18,920	38		
							1	:30	13.0	12	1,470	40	58,800	67		
							2	::	8.0	24	300	18	5,400	70		
							4	::	4.0							
							8	::	2.4							
							10	::	1.2							
							12	::	Trace							
10	M	25	156	Pulmonary tuberculosis	200,000	Intramuscularly	:	:30	10.5	2	825	70	57,750	28		
							1	::	12.0	4	200	61	12,200	35		
							1	:30	12.0	12	1,500	40	60,000	65		
							2	::	12.0	22½	690	7	4,800	67		
							4	::	6.3							
							8	::	1.2							
							10	::	1.0							
							12	::	Trace							
11	M	27	142	Pulmonary tuberculosis	200,000	Intramuscularly	:	:30	11.5	2	410	162	66,625	33		
							1	::	12.5	4	400	130	52,000	53		
							1	:30	12.5	12	800	68	54,400	86		
							2	::	9.0	24	284	32	9,088	91		
							4	::	4.8							
							8	::	Trace							
							12	::	0							
12	M	11	54	Cardiospasm	200,000	Intramuscularly	:	:30	22.5	2	35	1,500	52,500	26		
							1	::	22.5	4	36	1,000	36,000	44		
							2	::	17.5	12	110	350	38,500	63		
							4	::	9.0	24	237	42	9,954	68		
							8	::	3.0							
							12	::	Trace							
13	M	37	157	Pulmonary tuberculosis	500,000	Intramuscularly	:	:5	2.2	2	184	800	147,200	29		
							:	30	9.0	4	350	250	87,500	47		
							1	::	18.0	12	300	550	165,000	80		
							2	::	17.0	24	288	62	17,732	83		
							4	::	7.5							
							8	::	4.2							
							10	::	3.4							
							12	::	1.0							

(Pleural)

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No.	Sex	Age	Wt.	Diagnosis	Units	Route	Hr		Conc.	Hr					Fluid
14	M	16	94	Constrictive pericarditis; pleural and abdominal effusion	500,000	Intramuscularly	..	30	27.5	2	73	1,800	131,400	26	(Ascitic) 1 — Trace
							1	:	32.5	4	53	1,600	84,800	43	2 — 2.6
							1	30	25.0	12	228	500	114,000	66	4 — 3.0
							2	:	20.0	24	227	72	16,344.	69	6 — 4.0
							4	:	12.0						10 — 5.5
							6	:	8.5						(Pleural) 2 — 8.5
							10	:	3.0						4 — 11.5
							12	:	1.8						10 — 5.0
15	F	49	95	Pulmonary neoplasm; pleural effusion	500,000	Intramuscularly	..	30	30.0	2	190	575	109,250	22	(Pleural) 2 — 6.0
							1	:	32.5	4	115	375	43,125	30	4 — 9.5
							2	:	26.0						8 — 12.0
							3	:	20.0						12 — 7.0
							4	:	18.0						
							8	:	6.5						
							12	:	4.0						
16	M	42	108	Postoperative common duct obstruction; T tube in common duct; jaundiced	500,000	Intramuscularly	..	5	8.5	2	250	350	87,500	17	(Bile) 1 — 0
							1	:	30.5	5½	190	650	123,500	42	2 — 4.2
							1	30	21.0	12	510	100	51,000	52	3 — 7.0
							2	:	20.0						4 — 5.7
							3	:	12.0						6 — 5.5
							4	:	7.0						8 — 3.0
							8	:	3.0						10 — 1.7
							10	:	1.5						12 — Trace
							12	:	Trace						
17	M	26	172	Normal subject	500,000	Intramuscularly	..	5	2.5	2	185	550	101,750	20	
							1	30	16.0	4	60	1,050	63,000	33	
							1	:	17.0	8	260	450	117,000	56	
							2	:	18.0	12	245	225	55,125	67	
							3	:	16.0						
							4	:	12.0						
							8	:	10.0						
							10	:	4.5						
							12	:	3.5						
									2.5						

TABLE 3.—*Data on Absorption, Distribution and Excretion of Streptomycin—(Continued)*

Subject					Streptomycin		Serum			Urine					Other Body Fluids	
No.	Sex	Age	Weight, Lb.	Diagnosis	Dose, Units	Route	Time, Hr.	Time, Min.	Units per Cc.	Time, Hr.	Volume, Cc.	Units per Cc.	Units Excreted	% of Dose Excreted, Cumulative	Hr.	Units per Cc. (Bile)
18	F	32	129	Postoperative common duct stricture; T tube in common duct; not jaundiced	500,000	Intramuscularly	..	5	2.5	4½	370	700	259,000	51	2	8.0
							..	30	34.0	7½	200	100	20,000	55	4	10.0
							1	..	26.0	12	635	75	49,625	65	6	8.0
							1	30	26.0						8	4.2
							2	..	19.0						12	Trace
							3	..	13.0							
							4	..	8.0							
							8	..	3.5							
							12	..	Trace							
19	F	20	130	Pulmonary tuberculosis	100,000	Inhalation	..	30	0	2	160	0				
							1	..	0	8	160	0				
							2	..	0							
							3	..	0							
4	M	24	171	Pulmonary tuberculosis	200,000	Inhalation	..	5	0	6	720	3.5	2,520	1		
							..	30	0							
							1	..	Faint trace							
							2	..	0							
							6	..	0							
20	M	46	167	Hypopituitarism	400,000	Mouth	..	30	0	2	210	0				
							1	..	0	6	305	0				
							2	..	0	11	520	Trace				
							4	..	0	30	993	Trace				
							7	..	0							
							9	..	0							
							11	..	0							
21	F	50	124	Salmonella carrier	400,000	Mouth	1	..	0	24	...	0				
							2	..	0							
							3	..	0							
							6	..	0							
							9	..	0							
4	M	24	171	Pulmonary tuberculosis	500,000	Mouth	..	30	0	6	1,000	0				
							1	..	0							
							2	..	0							
							3	..	0							
							6	..	0							

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and for urine the mean percentage error is — 3.3 ± 2.1 per cent (standard deviation 11.15).

The subjects studied included ward patients and a few normal volunteers. There was no clinical evidence of impaired renal function in any one of these persons. Blood specimens were drawn from the antecubital veins and were, in most instances, allowed to clot, the serum being separated by centrifugation. In a few instances the blood was defibrinated with glass beads and the serum and cells handled separately. Urine was collected as voided specimens. All specimens were stored at approximately 5 C. until the determinations of streptomycin content could be run. In most instances the tests were made within forty-eight hours of collection, but occasionally a longer period of storage elapsed.

Streptomycin [13] was dissolved in sterile, pyrogen-free distilled water or 0.85 per cent sodium chloride solution in concentrations of 25,000, 50,000 and 100,000 units per cubic centimeter for single doses given intramuscularly or subcutaneously. The dose was dissolved in 10 or 20 cc. of 0.85 per cent saline solution when given as a single intravenous injection. For continuous intravenous or subcutaneous infusions the material was dissolved in either 0.85 per cent solution of sodium chloride or in 5 per cent dextrose solution in a concentration of 1,000 units per cubic centimeter. When given orally, the dose was placed in 200 cc. of tap water. Two patients received the material by inhalation of the nebulized material. The dose, dissolved in 4 cc. of water, was placed in a DeVilbiss no. 40 nebulizer, and the open end of the nebulizer was held just inside the lips, with the mouth open. Rubber tubing connected the nebulizer to a tank supplying oxygen at a flow of 6 liters per minute. A Y tube was placed in the tubing from the oxygen tank to the nebulizer so that the flow could be diverted during the expiratory phase of respiration. It required from forty to fifty minutes to complete the administration of the 4 cc. of solution.

OBSERVATIONS

Absorption and Excretion of Streptomycin Given by Various Routes. —This portion of the study was devoted largely to a consideration of the absorption and excretion of single doses of streptomycin. Serum levels were determined at intervals up to twelve hours following administration of the dose. Specimens of urine were collected whenever possible at two hours and four hours after giving streptomycin. The urine from four hours to twelve hours was pooled into a single specimen, as was the urine from twelve hours to twenty-four hours. Table 3 gives the data obtained in 25 experiments on 21 subjects who were given single doses of streptomycin.

In every instance in which a subject was given streptomycin parenterally it was possible to demonstrate the presence of the material in the serum. When the dose was 200,000 units or more, demonstrable amounts remained in the serum for twelve hours in virtually all subjects. As had been anticipated, the initial concentration in the serum

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13. The streptomycin used in these studies was supplied by Merck & Co., Inc. The material was partially purified, the active principle being present as the hydrochloride.

was considerably higher after intravenous than after intramuscular injection. Chart 1 shows the serum levels and the cumulative excretion in the urine when 100,000 units was given intravenously to 1 subject
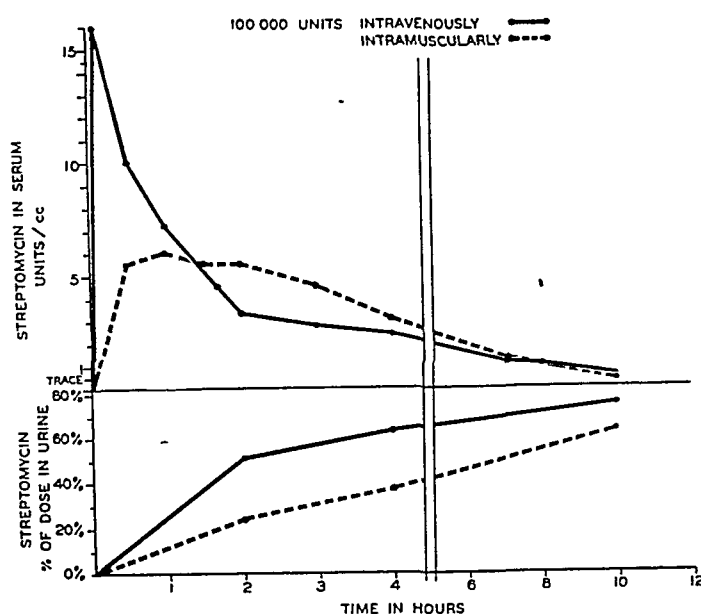
Chart 1.—Concentrations of streptomycin in the serum and the rate of urinary excretion following administration of 100,000 units intravenously (subject 2, table 3) and intramuscularly (subject 8, table 3).
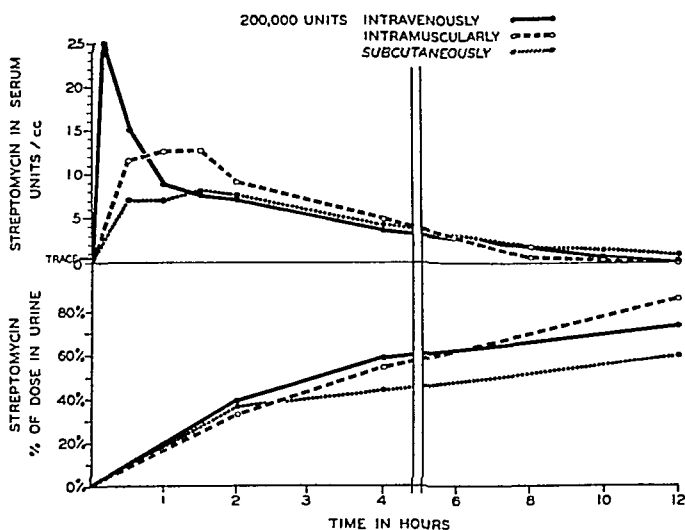
Chart 2.—Concentrations of streptomycin in the serum and the rate of urinary excretion following administration of 200,000 units intravenously (subject 4, table 3), intramuscularly (subject 11, table 3) and subcutaneously (subject 7, table 3).

and intramuscularly to another subject of approximately the same age and weight. Chart 2 gives the same data following the injection of 200,000 units intravenously, intramuscularly and subcutaneously for 3

subjects. In spite of significant initial differences, the serum levels were approximately the same at the end of two hours regardless of the route of administration. The peak levels in the serum were roughly proportional to the amount administered. This is illustrated in chart 3.

The rate of urinary excretion was greatest during the first two hours of observation at the time of highest serum levels. On the average, a larger percentage of the dose was excreted in the first two hours after intravenous than after intramuscular or subcutaneous dosage, but there was considerable overlap in individual cases. For the patients receiving streptomycin parenterally, the total excretion in twelve hours varied from 41 to 86 per cent of the dose, with a mean of 65 per cent. The
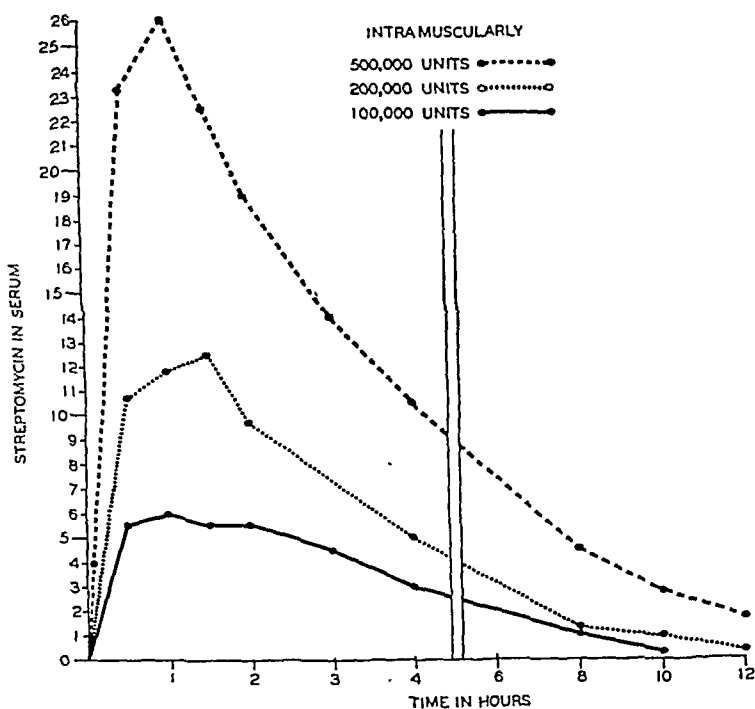
Chart 3.—Concentrations of streptomycin in the serum following varying doses given intramuscularly: 100,000 units to 1 subject, 200,000 units to 3 subjects (composite curve) and 500,000 units to 6 subjects (composite curve).

urine excreted between twelve and twenty-four hours after the injection usually contained only small additional amounts, varying from traces to 9 per cent of the dose.

The excretion of streptomycin in bile was studied on 2 patients who had undergone operation for obstruction of the common duct and had T tube remaining in the common duct (subjects 16 and 18, table 3). One patient (subject 16) was jaundiced; the other was not. Both received 500,000 units intramuscularly, and blood and urine were collected in the usual manner. Bile was collected by means of the T tubes. Chart 4 shows the levels in serum and bile at intervals during the twelve hours of study for subject 18. Unfortunately, it was impossi-

ble to be certain that the collection of bile was quantitative for either subject; hence calculation of the total excretion in the bile could not be made.

The oral administration of streptomycin in single doses of 400,000 and 500,000 units was not followed by any demonstrable serum level, and traces or none at all appeared in the urine. To 1 patient (subject 21, table 3) streptomycin was later given orally for six days in a dosage of 4,000,000 units per day (500,000 units every three hours). On this schedule, traces were noted in the serum in daily determinations and between 0.2 and 0.5 per cent of each day's dose was present in the twenty-four hour pooled specimens of urine. A stool obtained after three days on this dosage contained 8,700 units per gram of wet stool. The inhalation of streptomycin also failed to give rise to any appreciable level in the serum, and only small amounts appeared in the urine.
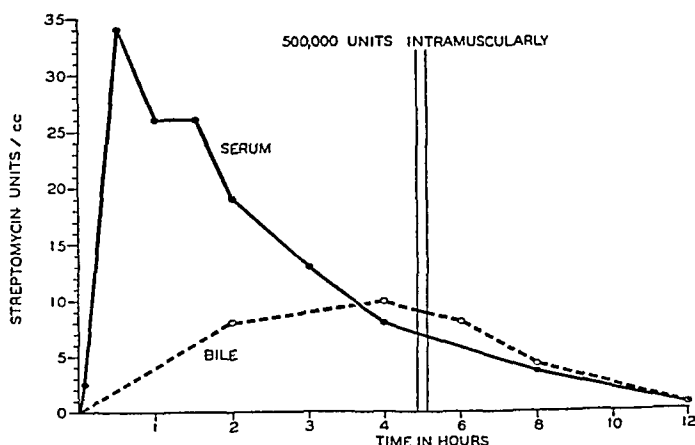
Chart 4.—Concentrations of streptomycin in the serum and in the bile following administration of 500,000 units intramuscularly (subject 18, table 3).

Distribution of Streptomycin.—Chart 5 shows the concentrations of streptomycin in serum, pleural fluid and ascitic fluid in a patient with constrictive pericarditis who received 500,000 units intramuscularly. Chart 6 shows the results of a similar experiment on a patient with a pulmonary neoplasm and an accompanying pleural effusion. In both subjects the level in the aberrant fluid rose as the serum levels fell and eventually exceeded the level in the serum.

On 2 subjects, blood was defibrinated and tests were run on serum and cells separately. There was no streptomycin demonstrable in the cells which had been hemolyzed by freezing, and the level in the serum obtained by this method was, within the limits of error of the method, the same as that in serum obtained by allowing the blood to clot.

A small number of data were collected regarding the diffusion of streptomycin into the spinal fluid. The subjects had received strepto-

mycin by repeated intramuscular injection
infusion for a period of twenty-four ho
blood and of spinal fluid were obtained
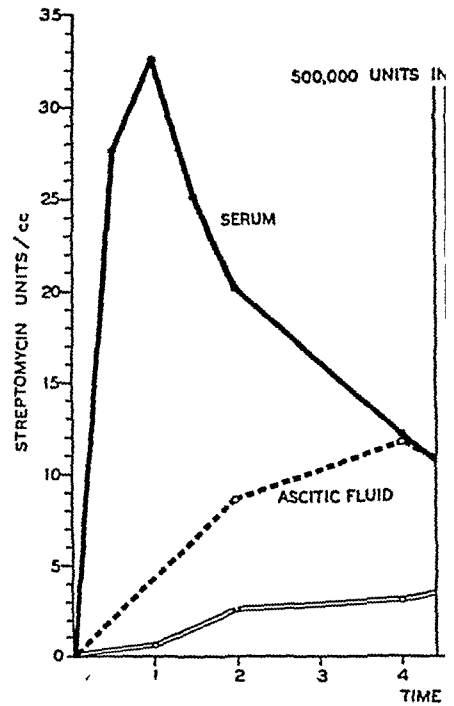
Chart 5.—Concentrations of streptomycin
fluid following administration of 500,000 units i
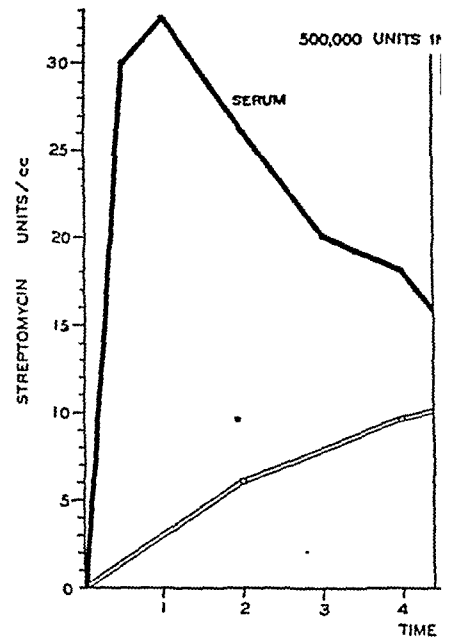
Chart 6—Concentrations of streptomycin i

meningitis and for 3 patients with definite meningitis are listed in table 4.

Two patients with tuberculous meningitis received streptomycin by continuous subcutaneous infusion in excess of forty-eight hours and extending to the time of death. Postmortem examinations were done within six hours after death, affording an opportunity to study the distri-

TABLE 4.—*Streptomycin in Serum and Spinal Fluid Taken Simultaneously*

Patient No.	Diagnosis	Streptomycin in Serum, Units/Cc.	Streptomycin in Spinal Fluid, Units/Cc.
1	Salmonella carrier.....................................	4.0	Trace
2	Pulmonary tuberculosis.............................	6.5	Trace
3	Infection of urinary tract...........................	25.0	2.0
4	Infection of urinary tract...........................	12.0	Trace
5	Tuberculous meningitis..............................	35.0	13.7
		17.5	12.0
		17.5	11.2
6	Tuberculous meningitis..............................	45.0	18.5
7	Hemophilus influenzae meningitis...................	16.0	4.5
		15.7	4.0
		17.5	12.5
		10.5	4.5

bution of streptomycin in the organs. Postmortem serum was obtained for purposes of comparison, and gallbladder bile was collected in 1 case. Weighed samples of the organs were ground with sand and a measured amount of isotonic solution of sodium chloride. The resultant mixtures were allowed to stand eighteen hours at refrigerator temperature, after which they were centrifuged and the supernatant fluid assayed. Table 5

TABLE 5.—*Distribution of Streptomycin in Body Fluids and Tissues Obtained Post Mortem*

Patient No.	Serum, Units per Cc.	Gallbladder Bile, Units per Cc.	Kidney, Units per Gm.	Lung, Units per Gm.	Heart Muscle, Units per Gm.	Brain, Units per Gm.	Liver, Units per Gm.
1	12	21	20	6	1	0	0
2	43	..	95	6	5	Trace	Trace

gives the results of assays with the concentrations in serum and bile expressed as units per cubic centimeter and in the organs as units per gram.

The Renal Excretion of Streptomycin.—The rate of urinary excretion of streptomycin is appreciably slower than that reported for penicillin,[14] a substance which has a similar origin and might be expected

14. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**:425, 1943.

to have a similar behavior. This difference is well illustrated in chart 7, which shows the serum levels and the rate of excretion in urine for both substances given intravenously. The subjects were young females of approximately the same height and weight. Penicillin determinations were done by a modification [15] of the Rammelkamp procedure.[16]

These sharp differences prompted the following experiments on the urinary excretion of streptomycin.

Two normal male subjects of average height and weight, without evidence of impaired renal function, were catheterized and given streptomycin by continuous intravenous infusion at carefully controlled rates for periods of two hours. The first ninety minutes of each period was allowed for the stabilization of plasma levels, and the urine was discarded. During the last thirty minutes of each
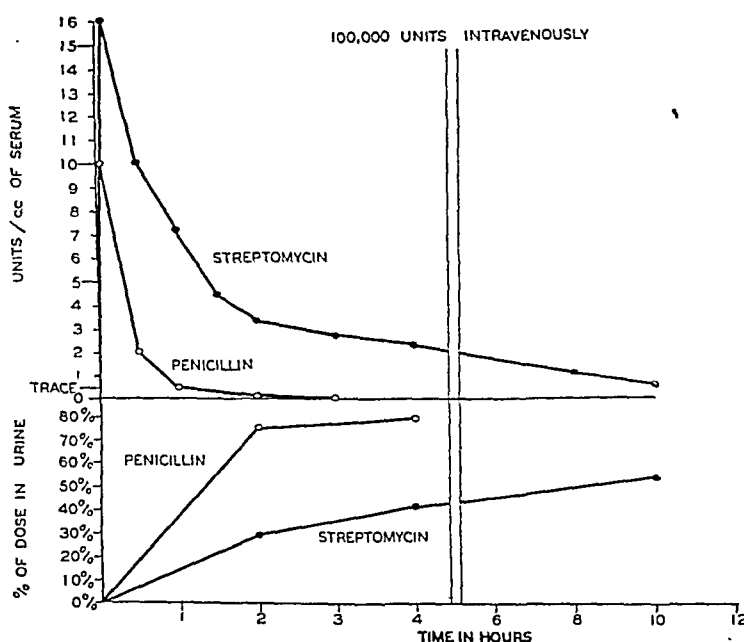
Chart 7.—Serum concentrations and rate of urinary excretion of streptomycin (1 subject) and penicillin (1 subject) following administration of 100,000 units intravenously.

period, a timed urine specimen was collected and a blood specimen was drawn. Immediately after the completion of·the first test period, the rate of infusion was doubled and the experiment was repeated in the same fashion. Determinations of the streptomycin content of the samples were made on the day of collection.

· The results of assay on these specimens, together with calculations of the plasma clearance values, are presented in table 6. From 38 to 67 cc. of plasma was cleared of streptomycin per minute, which is well

15. Kirby, W. M. M., and Rantz, L. A.: Methods of Measuring Penicillin Concentrations in Body Fluids, J. Bact. 48:603, 1944.

16. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Bio¹ & Med. 51:95, 1942.

within the 130 cc. per minute that might be expected of glomerular filtration alone.[17]   This adequately explains the observed differences in rate of excretion of streptomycin and penicillin, since it has been shown by Rantz and Kirby [18] that the plasma clearance values for penicillin are in the range of 750 to 1,120 cc. per minute.   There is also other indirect evidence [19] that penicillin is excreted by the tubules in addition to glomerular filtration.

TABLE 6.—*Urinary Excretion of Streptomycin During Continuous Intravenous Infusion*

Subject	Thirty Minute Test Period*	Infusion Rate, Units per Hour	Urine Volume, Cc.	Urine Excretion, Cc. per Min.	Concentration of Streptomycin		Plasma Cleared of Streptomycin, Cc. per Min.
					Urine, Units per Cc.	Plasma, Units per Cc.	
A	1	50,000	32.5	1.08	500	14	38
	2	100,000	48	1.60	800	19	67
B	1	125,000	122	4.66	187.5	13.5	64
	2	250,000	57	1.9	800	25	60

* Each thirty minute test period was preceded by a period of one and one-half hours during which the rate of infusion was the same as that of the test period.

COMMENT

The results reported here are in essential agreement with those of Reimann and his colleagues.[20]   The parenteral administration of streptomycin gave rise to serum levels which were roughly proportional to the amount injected.   On the other hand, oral dosage failed to give rise to any appreciable level in the serum.   The high concentration of streptomycin in the stool after oral administration indicates poor absorption rather than massive destruction or inactivation within the gastrointestinal tract.

After parenteral injection, from 41 to 86 per cent of the dose appeared in the urine during the first twelve hours with very small additional amounts thereafter.   This suggests that some of the material

17. Smith, H. W.; Goldring, W., and Chasis, H.:   The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263, 1938.

18. Rantz, L. A., and Kirby, W. M. M.:   The Absorption and Excretion of Penicillin Following Continuous Intravenous and Subcutaneous Administration, J. Clin. Investigation **23**:789, 1944.

19. Rammelkamp, C. H.:   Excretion of Penicillin in Man, Proc. Soc. Exper. Biol. & Med. **53**:30, 1943.   Beyer, K. H.; Woodward, R.; Peters, L.; Verwey, W. F., and Mattis, P. H.:   The Prolongation of Penicillin Retention in the Body by Means of Paraaminohippuric Acid, Science **100**:107, 1944.

20. Elias, W. F., and Durso, J.:   Blood, Urine and Fecal Levels of Streptomycin in the Treatment of Human Infections of E. Typhosa, Science **101**:859, 1945.   Reimann, Elias and Price.[9]

may be destroyed or inactivated within the body or in the urine itself. It seems unlikely that the amounts of streptomycin appearing in the bile could account for the discrepancy between the dosage and the urinary excretion.

In the assays conducted on organs obtained post mortem, the amounts of the drug in renal tissue were approximately double that in serum and smaller amounts were present in lung and heart muscle, while traces or none could be found in brain. It is perhaps of significance that the liver, an organ capable of altering many compounds, contained virtually no streptomycin.

The low plasma clearance values obtained for streptomycin explain its presence in the serum for as long as twelve hours following parenteral administration. It seems likely, however, that the high blood levels required in the treatment of infections [9] will necessitate frequent injections or continuous infusions in order that therapeutic levels may be maintained.

The data regarding diffusion of streptomycin into the spinal fluid are inconclusive and will require further elaboration before the therapeutic implications are clear. In the few studies reported here, it would seem that the presence of an inflammatory reaction in the meninges increases the diffusion of streptomycin into the spinal fluid.

SUMMARY

Data are presented regarding the absorption, distribution and excretion of streptomycin administered by various routes.

Streptomycin was not absorbed to any appreciable extent when given orally or by inhalation. Following parenteral administration, it was possible to demonstrate the material in the serum in amounts roughly proportional to the dose.

Streptomycin appeared in significant concentrations in the spinal fluid of 3 subjects with meningitis and in the pleural fluid of 2 subjects with pleural effusions. In 2 subjects streptomycin was demonstrated in the bile.

A study on the distribution of streptomycin in various organs obtained post mortem showed that it was present in the kidney in high concentration. Smaller amounts were found in the lung and in heart muscle, while both the brain and the liver contained virtually none.

From 41 to 86 per cent (mean 65 per cent) of the dose was excreted in the urine within twelve hours of the parenteral administration of streptomycin. Plasma clearance values ranged from 38 to 67 cc. of plasma cleared of streptomycin per minute.

Progress in Internal Medicine

BLOOD

A Review of the Recent Literature

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BONE MARROW

Osgood and Seaman[377] state after a review of the literature that wide discrepancies in the published values for normal marrow cells obtained by sternal puncture are due to uncritical acceptance of subjects as normal, differences in the quantity of material aspirated with a consequent variable degree of dilution of marrow with blood and lack of uniform criteria for identification of cells and terminology. They conclude that normal standards for aspirated marrow must await further studies. The authors advocate withdrawal of at least 1 cc. of material, since the cellular composition is not greatly affected by variations in volume in excess of 1 cc. The aspirated material should then be placed in a tube containing 2 mg. of potassium oxalate and thoroughly shaken. A count is made of nucleated cells, and films are prepared and stained with Wright's stain. Differential counts, which often are not necessary for diagnosis, should be made on at least 500 cells, utilizing the thin area of the film.

Two cases are reported by Schleicher[378] in which aspirated marrow revealed many giant orthochromatic erythroblasts. In 1 the diagnosis was reticulum cell sarcoma and in the other pernicious anemia. According to the author, such erythroblasts are not diagnostic of any disease but are an expression of a defunct reticulum. Interpretation of erythrogenesis should be based on the nuclear pattern of the early erythroid cells, including pronormoblasts and promegalo-

377. Osgood, E. E., and Seaman, A. J.: The Cellular Composition of Normal Bone Marrow as Obtained by Sternal Puncture, Physiol. Rev. 24:46, 1944.

378. Schleicher, E. M.: Giant Orthochromatic Erythroblasts: Their Importance for the Promegaloblast and Pronormoblast Problem, J. Lab. & Clin. Med. 29:127, 1944.

blasts. In another communication, Schleicher [379] states that the so-called azurophile granulation in the cytoplasm of proerythroblasts is essentially an artefact and indicates merely that the cells have reached a certain physicochemical phase·in their development.

Mitotic division of marrow cells was studied by Forteza Bover.[380] He concludes that although mitosis can be observed in the hemocytoblasts of acute leukemia it is rare, and consequently the rapid proliferation of the cells must be accounted for by amitotic division. Atypical mitosis in the erythrocyte series occurs in a variety of severe blood disorders. It may be characterized by fragmentation, fusion, asymmetry and multipolar division. De Barros [381] discusses the development of the erythrocyte·in normal circumstances and in pathologic conditions. He relates specific deficiencies to abnormalities of maturation and describes the resulting types of anemia. Vereby [382] advances the hypothesis that there exists in bone a substance which exerts a controlling influence on red marrow and is necessary for both the initiation and the maintenance of hemopoiesis.

Myeloid metaplasia associated with myelosclerosis is discussed by Oyanguren and Videla,[383] who review the literature dealing with this condition and report a case. Andersen and Lund [384] report a case of osteosclerotic anemia in a boy 17 months old. The clinical manifestations were anemia, fever and hemorrhages. Roentgen examination revealed pronounced periosteal deposits and large meshed structure of the substantia spongiosa. At necropsy extensive endosteal and periosteal osteosclerosis was found, together with fibrosis of the marrow. Many of the lymph nodes contained hemopoietic tissue, but there was no evidence of leukemia. Gormsen [385] reports 2 cases of myeloid metaplasia in the adrenal glands. In 1 case, that of a woman of 44 years, a single adrenal tumor consisting of hematopoietic tissue was found at necropsy. The patient died of a pulmonary embolus following hysterectomy for uterine fibroid. In the second case there was wide-

379. Schleicher, E. M.: Observations on the So-Called Azurophilic Granulation of Proerythroblasts, Anat. Rec. **87**:355, 1943.

380. Forteza Bover, J.: Estudio de las mitosis en las células de la serie roja y blanca de la médula ósea, Med. españ. **10**:790, 1943.

381. de Barros, N. V.: Fisiologia da eritropoiese, Folia clin. et biol. **14**:45, 1942.

382. Vereby, R.: Die Blutbildung im Knochenmark und die Knochensubstanz, Deutsche med. Wchnschr. **69**:660, 1943.

383. Oyanguren M., H., and Videla Z., P.: Anemia leuco-eritroblástica esplenomegálica del adulto por mieloesclerosis, Rev. méd. de Chile **71**:896, 1943.

384. Andersen, B., and Lund, T.: Osteosclerotic Anemia in a Boy of 17 Months, Acta path. et microbiol. Scandinav. **20**:425, 1943.

385. Gormsen, H.: ·Ueber das Vorkommen von hämopoietischem Gewebe in der menschlichen Nebenniere, Virchows Arch. f. path. Anat. **310**:369, 1943.

spread myeloid metaplasia with hemopoiesis occurring in both adrenal glands.

The characteristics of the marrow of a series of 100 elderly patients are reported by Reich, Swirsky and Smith.[386]   They observed active hemopoiesis in these subjects, with no evidence of myeloid atrophy attributable to age.   Cope [387] discusses the value of sternal aspiration as a diagnostic aid.   Linhard [388] found that in cases of trypano-somiasis the organisms were much more numerous and more readily found in aspirated sternal marrow than in the peripheral blood.   Meyer and Halpern [389] report the case of a 51 year old man with chronic myelogenous leukemia and myocardial disease, who died immediately after sternal puncture, apparently from cardiac failure.

Bloom and Meyer [390] present tables of normal cellular constituents of the marrow and peripheral blood of dogs.   The specimens of marrow were obtained from the crest of the ilium.   Yoffey and Parnell [391] obtained an average value of 469,000 nucleated cells per cubic milli-meter of rabbit costal marrow, of which 61,000 were lymphocytes.   Their data, it is concluded, lend support to the view that lymphocytes leave the blood to enter the bone marrow but they throw no light on the fate of the lymphocytes in the marrow.

<center>LIPOID HISTIOCYTOSES</center>

Niemann-Pick's Disease.—Canmann [392] reports a case of Niemann-Pick's disease and reviews much of the literature dealing with the subject.   To date somewhat more than 60 cases of this disease have been reported.   About half the patients have been members of the Jewish race, and in about one fourth of the cases there was a positive family history of the disorder.   The disease has been uniformly fatal before the age of 30 months.   The cherry red macular spot which occurs in both this disease and in Tay-Sachs disease is a helpful

386. Reich, C.; Swirsky, M., and Smith, D.:   Sternal Bone Marrow in the Aged, J. Lab. & Clin. Med. **29**:508, 1944.

387. Cope, R. L.:   Sternal Marrow Aspiration as an Aid in Diagnosis, Texas State J. Med. **40**:191, 1944.

388. Linhard, J.:   Value of Sternal Puncture in Diagnosis of Trypanosomiasis, Trop. Dis. Bull. **41**:14, 1944.

389. Meyer, L. M., and Halpern, J.:   Death Following Sternal Puncture, Am. J. Clin. Path. **14**:247, 1944.

390. Bloom, F., and Meyer, L. M.:   The Morphology of the Bone Marrow Cells in Normal Dogs, Cornell Vet. **34**:13, 1944.

391. Yoffey, J. M., and Parnell, J.:   The Lymphocyte Content of Rabbit Bone Marrow, J. Anat. **78**:109, 1944.

392. Canmann, M. F.:   Niemann-Pick Disease (Acute Idiopathetic Xanthoma-tosis, Phosphatide Lipoidosis, Lipoid Cell Splenomegaly, Niemann Type), J. Pediat. **24**:335, 1944.

diagnostic sign. The pathogenesis of the disease is still open to investigation.

Canmann's patient was an infant who died at the age of 10 weeks, having been ill from the time of birth. The clinical diagnosis was congenital heart disease and hypothyroidism. At autopsy the heart and liver were found to be twice the normal size and the spleen three times normal size. Microscopic examination showed dissemination and infiltration of foam cells in all the organs and in the bone marrow.

Facatselli[393] summarized the clinical findings in Niemann-Pick's disease, discussed the interrelationships among the lipoid diseases, including Tay-Sachs disease, and reported a case of Niemann-Pick's disease in detail. His patient was a 14 month old girl, the first child of native Turks. There was no knowledge of familial diseases. The infant was well and strong until the age of 8 months, when progressive enlargement of the abdomen with failure of further body growth appeared. Examination showed the girl to be poorly nourished. The ocular fundi were normal and the inguinal lymph nodes moderately enlarged. There was an enormous enlargement of the spleen and liver. The examination of the peripheral blood showed the hemoglobin content to be 35 per cent and the red blood cells 2,700,000. The red blood cells showed great variation in staining and in size and shape, and a few were nucleated. Giant foam cells were obtained from the spleen, bone marrow and lymph nodes by puncture. Five-tenths cubic centimeter of splenic pulp was aspirated and subjected to a chemical analysis, which showed 2.74 per cent phosphatides and 0.046 per cent cerebrosides. The blood cholesterol level was 280 mg. per hundred cubic centimeters. The child finally died of an intercurrent infection at the age of 2½ years.

Von Cube, Schmitz and Wienbeck[394] report another case of Niemann-Pick's disease. The authors point out that this malady often cannot be diagnosed during life or distinguished from the infantile form of Gaucher's disease. The central red area in the macula is the only clinical sign differentiating the two diseases. They reported the case of a 2 year old child, the fourth and last sibling in a non-Jewish family. There were no known familial diseases. At the age of 9 months failure of the patient to gain weight led to the discovery of gross enlargement of the liver and spleen. The blood values, except for a leukopenia of 4,600, were normal. At the age of 1 year and 10 months the patient's development was further retarded and there was a serious feeding problem. At this time a moderately severe

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393. Facatselli, N.: La maladie de Niemann-Pick (apropos d' un cas personnel), Ann. pædiat. **162**:218, 1944.

394. von Cube, R.; Schmitz, E., and Wienbeck, J.: Leichte bis mittelschwere Niemann-Picksche Krankheit, Virchows Arch. f. path. Anat. **310**:631, 1943.

hypochromic anemia was present, but sternal aspiration revealed normal marrow. The child died during an operation for removal of the spleen.

The spleen and brain were subjected to chemical analysis. A phosphatide, largely insoluble in ether, and cholesterol accounted for 91 per cent of the total lipids in the spleen. Microscopic study of the tissues revealed characteristic features of the disease, but they were less extensive than those in most reported cases. The brain showed no outstanding abnormalities.

Gaucher's Disease.—Fanconi [395] reported 2 cases of Gaucher's disease occurring in non-Jewish, healthy families. The first patient was a 5 year old girl who had enlarged lymph nodes and who became slightly jaundiced. Examination showed the liver and spleen to be enlarged, the lower borders lying some 5 cm. below their respective costal margins. The blood was normal, and tests of hepatic function showed no impairment of function. The blood cholesterol value was 362 mg. per hundred cubic centimeters. Both sternal puncture and splenic puncture revealed the presence of large Gaucher's cells. Roentgenograms of the skeleton were normal. His second case was a follow-up study of an 18½ year old girl whose spleen had been removed earlier in life because of Gaucher's disease. Her general condition had remained poor. Examination showed that she was poorly developed, infantile in build and slightly icteric. The edge of the liver lay 10 cm. below the right costal margin. There was a slight 'anemia present, and sternal aspiration revealed an infiltration of the bone marrow by Gaucher's cells. Roentgenograms of the chest showed that there was increased density in both pulmonary fields. There was thinning of the cortex and widening of the trabeculae in the ribs and in the carpal bones such as are seen in Cooley's anemia. The blood cholesterol level varied from 645 to 683 mg. per hundred cubic centimeters, more than double the preoperative level. The serum phosphatides were 36.8 mg. per hundred cubic centimeters, whereas the preoperative value was 18 mg. The author observed that the more frequently cases of lipoid disease are studied the less sharply defined are the various clinical types. In Gaucher's disease, since there is no alteration in the fundamental process accomplished by splenectomy, this operation should be delayed as long as possible.

Stehle [396] discussed at length the effect of splenectomy in Gaucher's disease, both the immediate effect and the long range influence on the natural course of the disease. He reported a late follow-up study of 2 cases in which splenectomy had been done early in life. His

395. Fanconi, G.: Zwei Fälle von Morbus Gaucher, Ann. pædiat. **162**:270, 1944.

396. Stehle, I.: Beiträge zur Morbus Gaucher: II. Die Folgen der Splenektomie beim Morbus Gaucher, Deutsche Ztschr. f. Verdauungskr. **7**:145-1943.

observations suggest that the skeletal changes which sometimes occur are a constitutional variant having no direct relation to forms of the disease characterized by splenomegaly and hepatomegaly. Splenectomy is beneficial in that it rids the patient of a bulky organ, and in many cases there has followed great improvement in the anemia, leukopenia and hemorrhagic tendency. The operation is regarded as a symptomatic measure in the treatment of this disease.

Levine and Solis-Cohen [397] observed a 29 year old woman in whom a slight injury produced a fracture of the humerus. A roentgenogram showed multiple areas of punctate osteolysis in the cortical and medullary portions of the shaft, with some destruction of the cortex and periosteum at the neck of the humerus. Similar lesions were widely spread throughout the opposite humerus as well as in the other long bones and in the skull. A biopsy from the fractured bones showed cells typical of Gaucher's disease.

Hand-Schüller-Christian Disease.—Many new cases of Hand-Schüller-Christian disease and the recently recognized variant of that disease, eosinophilic granuloma of bone, have been reported during the past year. Garrahan and his collaborators [398] had under their care a 2 year and 5 months old boy in whom an orbital tumor developed, with exophthalmos and polyuria. The urine and blood were normal. Multiple osseous lesions were demonstrated, and later a granulomatous cutaneous tumor developed. A biopsy was made and a diagnosis of Schüller-Christian's disease established, although the histologic observations were not entirely typical. Baeza Goñi and Espinoza Soto [399] report a fatal case of this disease in a 3 year old boy who had generalized enlargement of the lymph nodes and diabetes insipidus associated with cachexia. At autopsy lipoid cellular infiltrations were found in the lymph nodes, hypophysis, liver, spleen and bone marrow.

Michaud and Sorba [400] reported an unusual instance of cholesterosis with multiple localizations in a 34 year old woman. Her illness began with generalized cutaneous pruritus and jaundice. Fatigue and rarely a slight fever occurred. Examination showed diffuse xanthomatosis of the skin and mucous membranes and enlargement of the liver. Roentgenograms showed a bony defect at the vertex of the skull, but

397. Levine, S., and Solis-Cohen, L.: Gaucher's Disease, Am. J. Roentgenol. **50**:765, 1943.

398. Garrahan, J. P.; Lascano González, J. C.; Gambirassi, A., and Magalhaes, A.: Sobre el granuloma eosinófilo y la enfermedad de Hand-Schüller-Christian, Arch. argent. de pediat. **22**:3, 1944.

399. Baeza Goñi, A., and Espinoza Soto, J.: Reticuloendoteliosis lipoidica (enfermedad de Hand-Schüller-Christian atípica), Rev. chilena de pediat. **15**:437, 1944.

400. Michaud, L., and Sorba, M.: Cholestérinose à localisations multiples, Schweiz. med. Wchnschr. **73**:1184, 1943.

the bones were otherwise normal. The circulating blood values were normal except for 8 per cent reticulocytes. Sternal aspiration revealed an abundance of cells with xanthomatous inclusions. Several determinations of the blood cholesterol level ranged from 8.5 to 20 Gm. per thousand cubic centimeters. A biopsy of the skin showed a heavy infiltration of xanthomatous cells closely grouped about the blood vessels and under the epidermis. The authors regarded the case as an atypical form of the Hand-Schüller-Christian disease.

An authoritative and thorough review of the subject of eosinophilic granuloma of bone was published by Jaffe and Lichtenstein.[401] Their work has shown that in this disease one, several or many bones may be affected but that the disease is limited to the bony tissue. They believe that this entity is the mildest expression of the peculiar inflammatory histiocytosis which occurs also in the more serious disease described under the names of Letterer-Siwe and Schüller-Christian. The changes in the blood are limited to an occasional instance of leukocytosis of moderate severity or to such changes as a slight increase in the eosinophilic granuloma developing under the mandible of a 24 year old man. There was an eosinophil count of 7 per cent in the case of this patient. The tumor was excised completely, and the patient remained well. Microscopic examination of the specimen showed that the granuloma had originated about a rudimentary tooth rest. Inclán and León [402] reported 2 cases of eosinophilic granuloma of bone in girls 3 years and 10 months old and 11 months old. The diagnosis was proved by biopsy in both cases. Examinations of the blood showed an eosinophilia of 3 to 4 per cent, and in 1 case the Rumpel-Leede phenomenon appeared.

Versiani, Figueiró and Junqueira [403] reported the occurrence of an eosinophilic granuloma of bone in a 50 year old Spanish woman. The first symptoms were stabbing pains in the left thigh. A roentgenographic examination showed a fusiform area of rarefied bone in the middle of the left femur, and for a time the patient's painful symptoms were relieved by antisyphilitic treatment. Nine months later, while hurrying to catch a train, she suffered a fracture through the diseased area of bone. A polyuria of over 5 liters per day was noted and success-

401. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: A Condition Affecting One, Several or Many Bones, but Apparently Limited to the Skeleton, and Representing the Mildest Clinical Expression of the Peculiar Inflammatory Histiocytosis also Underlying Letterer-Siwe Disease and Schüller-Christian Disease, Arch. Path. **37**:99 (Feb.) 1944.

402. Inclán, A., and León, P. M.: Granuloma eosinófilo de los huesos, Cir. ortop. y traumatol., Habana **11**:58, 1943.

403. Versiani, O.; Figueiró, J. M., and Junqueira, M. A.: Hand-Schüller-Christian's Syndrome and "Eosinophilic or Solitary Granuloma of Bone," Am. J. M. Sc. **207**:161, 1944.

fully treated with posterior pituitary extract. Biopsy of the lesion in the femur showed granulomatous tissue infiltrated with eosinophils. There was no other bony lesion demonstrable by roentgenographic examination. In five months' time another examination showed slow, aberrant formation of bony callosity in the region of the fracture.

An eosinophilic granuloma producing neurologic signs and symptoms was reported by Osborne, Freis and Levin.[404] A 21 year old soldier had first a transient paralysis of the side of the face and four months later an acute attack of vertigo, at which time tenderness over the spine of the first thoracic vertebra was found. Tinnitus and pain in the ear developed subsequently. Roentgenograms of the skull showed destructive lesions in the left temporal bone, the mandible, the first, second and seventh cervical vertebrae, several ribs, the right femur and the transverse process of the fifth lumbar vertebra. There was no abnormality of the circulating blood except for an increased sedimentation rate. Two specimens for biopsy were taken from the mandible and one from the fifth rib. In each specimen there ·was destruction of bone and replacement with a gray granulation tissue, and microscopically the typical changes of eosinophilic granuloma were seen. Roentgen ray therapy was given, and four months later, eleven months after the initial symptoms, he was free of neurologic signs and symptoms and there was partial recalcification of the bony defects.

Thoma [405] treated an 8 year old child who had a fleshy tumor with destruction of the bone in the mandible and later with other destructive areas in the mandible, skull and pubic bone. Diabetes insipidus appeared. A biopsy of the mandible showed eosinophilic granuloma. Roentgen ray therapy was followed by definite improvement.

HEMORRHAGIC DISORDERS AND COAGULATION OF BLOOD

· *General Observations.*—The factors and mechanisms involved in the coagulation of blood continue to engage the interest of many investigators. Recent studies have been concerned not only with the factors having to do with the production of a clot but also with those which prevent coagulation in vivo. However, precisely what acts as the trigger in initiating coagulation and whence this substance is derived are still not known. Quick [406] reviews the literature that

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404. Osborne, R. L.; Freis, E. D., and Levin, A. G.: Eosinophilic Granuloma of Bone Presenting Neurologic Signs and Symptoms: Report of a Case, Arch. Neurol. & Psychiat. **51**:452 (May) 1944.

405. Thoma, K. H.: Eosinophilic Granuloma with Report of One Case Involving First the Mandible, Later Other Bones, and Being Accompanied by Diabetes Insipidus, Am. J. Orthodontics (Oral Surg. Sect.) **29**:641, 1943.

406. Quick, A. J.: Blood, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1944, vol. 6, p. 295.

has appeared since his excellent monograph in 1941. He emphasizes the controversy attendant on the commonly accepted theories as to the mechanism of coagulation and reviews the current status of knowledge regarding prothrombin, platelet activity and the various anticoagulants. He reports further experimental evidence [407] that prothrombin is composed of two factors, A and B, which are combined through calcium. The factor which disappears in decalcified stored blood is designated component A. Component B is the factor which disappears after feedings of dicoumarin and in vitamin K deficiency. Therefore stored blood and plasma should be effective in treating the hypoprothrombinemia produced by dicoumarin.

Quick was able to confirm the work of Bay, Tanturi and Banfi,[408] who found that peptone shock, induced in dogs by Witte's peptone, was accompanied with an increase in the coagulation time. This increase and its persistence varied directly with the dose of peptone used. Reinjection of peptone into an animal after twenty-four hours showed that the first injection had produced a relative state of immunity as far as modification of coagulation time was concerned. An anticoagulant, probably heparin, was thought to be liberated on the injection of the peptone. No alteration in prothrombin concentration was demonstrated.

Antithrombin content of the blood and its relation to heparin are also discussed by Volkert,[409] who noted that on intravenous injection of solutions of albumin antithrombin increases of 60 to 70 per cent, lasting two or three hours, occurred experimentally. Subsequent injections resulted in transient increases of only 10 per cent in antithrombin. Volkert considers that this change in antithrombin is related to hypersensitivity. The injection of pneumococcic antigen or other protein as well as anaphylactic reactions caused transient increases in the antithrombin content of the blood. The role of histamine as an anticoagulant has been considered by de Takáts,[410] who investigated the effect of stimulating the cholinergic and adrenergic components of the autonomic nervous system on the clotting mechanism. Adrenergic stimuli were observed to increase and cholinergic stimuli to decrease the tendency to postoperative thrombosis. These phenomena were thought to be correlated with the fact that histamine closes and epinephrine

407. Quick, A. J.: Constitution of Prothrombin and Its Clinical Significance, J. A. M. A. **124:**734 (March 11) 1944.

408. Bay, R.; Tanturi, C. A., and Banfi, R. F.: El tiempo de coagulación y la protrombina en el shock peptónico, Medicina, Buenos Aires **4:**267, 1944.

409. Volkert, M.: Der Antithrombingehalt des Blutes und seine Beziehung zum Heparin, Biochem. Ztschr. **314:**34, 1943.

410. de Takáts, G.: Nervous Regulation of Clotting Mechanism, Arch. Surg. **48:**105 (Feb.) 1944.

opens the sphincters controlling venous outflow from the liver. Since plasma prothrombin is manufactured to a great extent in the liver, it is possible that by neurogenic control the rate of its discharge from the liver may be influenced, with falls in plasma prothrombin with histamine stimulation, shock and anaphylaxis and rises in plasma prothrombin with epinephrine stimulation, excitement and fear.

Antithrombin is believed to consist of two components, one variable and the other constant. The exact nature of either is unknown, but de Sütö-Nagy [411] presents evidence in support of the theory that sphingomyelin, derived from tissue albumin, may be a natural antithromboplastin, or thrombin inhibitor. Removal of sphingomyelin, or inactivation of thromboplastin and calcium, may be the necessary first step for the activation of thrombin in setting off the coagulation mechanism. Feissly [412] believes that the classic theory of coagulation of the blood, in which prothrombin activation is attributed entirely to the disintegration products of platelets under set circumstances, must be seriously doubted. He has been able to confirm the presence in normal plasma of a prothrombin activator which differs from the prothrombin activator obtained from platelet extract. The former is thermolabile and probably protein in nature; the latter is thermostabile and probably a lipid. He suggests, therefore, that, whereas platelets and their disintegration products are capable of accelerating the clotting process, other factors are concerned in its initiation. Further studies along this line of reasoning have been conducted by Adams following the observation of Parfentjev in 1941 that a pseudoglobulin fraction obtained from plasma from rabbits had a pronounced coagulative activity on normal human oxalated blood. This pseudoglobulin fraction showed excellent hemostatic activity in small wounds. When the substance was given by mouth in large doses, a decrease in the coagulation time of the circulating blood was noted. The more recent study by Adams and Taylor [413] shows that plasma from both beef and swine may be used as a source of a pseudoglobulin possessing thrombic activity similar to that of plasma from rabbits but that preparations from these animals require more purification than do those from rabbits.

Under physiologic conditions, calcium is indispensable for coagulation of the blood. Although oxalated plasma will not clot spontaneously, it has been known that contamination with certain organisms,

411. de Sütö-Nagy, G. J.: Mode of Action of Anti-Coagulant Derived from Tissues, Am. J. Physiol. 141:338, 1944.

412. Feissly, R.: Sur la thrombokinase plasmatique, Helvet. med. acta 10:3, 1943.

413. Adams, M. A., and Taylor, F. H. L.: The Thrombic Activity of a Globulin Fraction of the Plasma Proteins of Beef, Swine and Human Blood, Am. J. M. Sc. 205:538. 1943.

such as staphylococci, will produce coagulation. Fredericq [414] reports studies concerning this type of coagulation in the absence of calcium and concludes that the coagulase produced by the bacteria replaces thrombin in the clotting mechanism and directly activates fibrinogen. The relation, if any, of coagulase to thrombin is unknown.

Since 1938 there have appeared in the literature reports dealing with the presence in acetone extracts of spleens from patients with idiopathic thrombopenic purpura of a substance which would cause a definite transient lowering of platelets when injected into rabbits. Cronkite [415] believed he was able to confirm the presence of "thrombocytin" in extracts of spleens removed from patients with idiopathic thrombocytopenic purpura and from 1 patient with chronic malignant neutropenia, but from extracts of spleens of patients with tuberculosis of the spleen, clinically indistiguishable from idiopathic thrombocytopenic purpura, no such effect was obtained.

Werner [416] has studied the blood platelets and clot retraction and reports that the retraction ferment of platelets cannot be extracted.

Øllgaard [417] observed that if citrated blood is allowed to settle at 42 C. for three hours and if small 'amounts of mercuric cyanide or saponin are then added platelet agglutination develops to so pronounced a degree as to be macroscopically visible. The degree of agglutination among normal persons was observed to be extremely variable. In women up to the thirtieth year it is strongest. The addition of heparin to the plasma completely inhibits the platelet-agglutinating activity of mercuric cyanide and saponin.

A definite clinical contribution is the work of G. and R. Reimann-Hunziger,[418] who studied the effect of surgical procedures on the platelet counts of 30 patients. Counts were done immediately before operation and one hour and three days after operation. The type of illness, operation or anesthesia did not appear to influence the counts. Although most patients showed a slight increase in the number of platelets immediately postoperatively, their values dropped to normal by the third day. The author believes that those patients showing thrombocytosis as late as the third day should be considered as candidates for prophylactic heparinization because of the potential danger of pulmonary embolism.

414. Fredericq, P.: La coagulation du sang en l'absence de calcium, Arch. internat. de physiol. **52**:73-152, 1942.

415. Cronkite, E. P.: Further Studies of Platelet Reducing Substances in Splenic Extracts, Ann. Int. Med. **20**:52, 1944.

416. Werner, H.: Strukturgebundene Fermentwirkung der Thrombozyten, Deutsche med. Wchnschr. **70**:155, 1944.

417. Øllgaard, E.: Untersuchungen über die Agglutination der Blutplättchen, Klin. Wchnschr. **22**:80, 1943.

418. Reimann-Hunziger, G., and Reimann-Hunziger, R.: Ueber das Verhalten der Blutplättchen vor und nach Operationen, Wien. klin. Wchnschr. **57**:62, 1944.

An unusually interesting study is that of de Takáts, Trump and Gilbert,[419] who, because of the frequent observation of the sudden development of embolic phenomena in patients who have had auricular fibrillation for many years and because of the fact that some of these patients had been receiving digitalis, studied the effect of digitalis on the clotting mechanism. With use of the heparin tolerance test, digitalis was shown to have a counteracting effect on the anticoagulant activity of heparin in both animals and human beings. The mechanism by which digitalis opposes heparin in the coagulation system is not known. Specific thromboplastic properties or efficiency in mobilization of prothrombin from the liver are suggested.

Massie and others [420] also report that the administration of digitalis causes a decrease in the clotting time of the blood. In studying 35 patients of both sexes, with and without heart disease, ranging in age from 24 to 78 years, Massie and his associates could demonstrate no alteration in prothrombin time or in clot retraction before and after digitalization. The general condition of the patient, degree of reaction to the drug and presence or absence of failure had no detectable effect on the coagulation-accelerating effect of digitalis. It is suggested that the digitaloid drugs may have a thromboplastic effect because of some specific action antagonistic to heparin.

A technic for the determination of increased coagulability of the blood to be used as an adjunct in the study of thrombosis in digitalized patients is described by Waugh and Ruddick.[421]

Shapiro [422] describes a single stage method of prothrombin estimation of great sensitivity, which he advocates for serial estimations for postoperative and postpartum patients for the early detection of a thrombogenic state (reactive hyperprothrombinemia) in order that anticoagulant therapy may be instituted early and extension of thrombotic processes be avoided.

Purpura.—There have been but few publications and no important new contributions dealing with essential thrombopenic purpura in the past year. Limarzi [423] and Farrar and Roxby [424] have published gen-

419. de Takáts, G.; Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on the Clotting Mechanism, J. A. M. A. **125**:840 (July 2) 1944.

420. Massie, E.; Stillerman, H. S.; Wright, C. S., and Minnich, V.: Effect of Administration of Digitalis on Coagulability of Human Blood, Arch. Int. Med. **74**:172 (Sept.) 1944.

421. Waugh, T. R., and Ruddick, D. W.: Test for Increased Coagulability of Blood, Canad. M. A. J. **50**:547, 1944.

422. Shapiro, S.: Hyperprothrombinemia, Premonitory Sign of Thrombo-Embolization (Description of Method), Exper. Med. & Surg. **2**:103, 1944,

eral papers on purpura, reviewing the current status of diagnosis and management of the thrombopenic purpuras particularly. Farrar and Roxby stress the necessity for complete etiologic diagnosis, reiterating that splenectomy is indicated only in treatment of patients with idiopathic thrombopenic purpura. In treatment of secondary purpuras therapy consists of amelioration or correction of the primary difficulty. Kracke [425] believes transfusion of fresh whole blood is the medical method of choice in staying bleeding. With the use of prophylactic transfusions White [426] reports the uneventful extraction of a tooth from a patient with long-standing severe thrombopenic purpura. Whether or not the thrombopenia was primary is not stated. Emphasis is placed on the major surgical hazards which even minor procedures in these patients present.

Purpura as a complication of pregnancy and the probable status of the children born of such mothers continue to be subjects of concern to the internist, surgeon, obstetrician and pediatrician alike. The paucity of available reports precludes any gross generalizations, but from the report of Burnett and Klass [427] it is apparent that it is possible for a pregnancy complicated by purpura to terminate in the birth of a healthy child with normal blood values. Finn [428] believes the likelihood of having a normal baby is best if the disease is in a chronic phase or if splenectomy is done prior to pregnancy. His opinion is based on the study of 13 cases of thrombopenic purpura complicated by pregnancy, in which there were 5 infant deaths. However, only 1 of these could be attributed to congenital thrombopenic purpura. Of the 8 surviving infants, 1 had frank bleeding and 1 had petechiae. Polowe [429] reports a case of pregnancy complicated by thrombopenic purpura successfully treated by splenectomy in the eighth month of gestation. The patient gave birth twelve days later to a small but normal infant.

423. Limarzi, L. R.: Hemorrhagic Diseases, Dent. Outlook **31**:142, 1944; Thrombocytopenic Purpura, M. Clin. North America **28**:153, 1944.

424. Farrar, G. E., Jr., and Roxby, J. B., Jr.: The Management of Purpura, Clinics **2**:1295, 1944.

425. Kracke, R. R.: Diagnosis and Treatment of the Bleeding Diseases, J. South Carolina M. A. **40**:1, 1944.

426. White, J. W.: Thrombocytopenic Purpura and Tooth Extraction, Brit. M. J. **2**:341, 1944.

427. Burnett, C. W. F., and Klass, I.: A Review of the Problem of Purpura During Pregnancy, J. Obst. & Gynaec. Brit. Emp. **50**:393, 1943.

428. Finn, W. F.: Thrombocytopenic Purpura in Pregnancy: Review of the Literature with a Report of Three Cases, Am. J. Obst. & Gynec. **48**:497, 1944.

429. Polowe, D.: Splenectomy in Pregnancy Complicated by Thrombocytopenic Purpura Hemorrhagica: Report of a Successful Case, with a Review of the Literature, J. A. M. A. **124**:771 (March 18) 1944.

Unusual instances of symptomatic thrombopenic purpura include those reported by Pérez Castañeda,[430] who had 4 patients with vitamin C deficiency associated with thrombopenia and bleeding. The intravenous administration of ascorbic acid was followed by increased platelet counts and the cessation of bleeding.

Conklin and Shank [431] report a case of thrombopenic purpura complicating exophthalmic goiter in a 36 year old woman. Unfortunately the patient's condition precluded studies of the bone marrow. However, no pathologic cells were found in the blood. After surgical removal of the thyroid, although thrombopenia persisted, the patient became asymptomatic.

Woodward [432] reports the occurrence in a 14 year old boy of acute catarrhal jaundice complicated by thrombopenic purpura and followed by an uneventful recovery with conservative management. He considers that the thrombopenia was due not to impaired hepatic function alone but to a general disturbance of the reticuloendothelial tissue associated with generalized lymphadenopathy and splenomegaly. In a search of the literature he found the report of only 1 similar case.

Rhodes and Borelli [433] report an instance in an infant of giant hemangioendothelioma (confirmed by biopsy) associated with thrombopenic purpura. High voltage roentgen therapy caused regression of the tumor mass and restoration of the blood picture to normal.

Purpura as a complication of malaria is reviewed by Greco and Ziedman.[434] They report a case of purpura symptomatica (Henoch-Schönlein type) complicating therapeutic quartan malarial fever. The drugs the patient received before purpura developed, bismuth subsalicylate, sodium chloride and dextrose and a mixture of acetylsalicylic acid, acetophenetidin and caffeine, were exonerated, because they were readministered after his recovery without ill effect. Quinacrine hydrochloride, first given after the onset of purpura, failed to stop the progress of the lesions or to control the malaria. Quinine promptly halted the malarial

430. Pérez Castañeda, L.: Avitaminosis púrpuro-hemorrágica, Med. españ. **4**:193, 1940.

431. Conklin, S. D., and Shank, P. J.: Thrombocytopenic Purpura Associated with Exophthalmic Goiter: A Review of the Available Literature and a Case Report, Ohio M. J. **40**:47, 1944.

432. Woodward, T. E.: Thrombocytopenic Purpura Complicating Acute Catarrhal Jaundice: Report of a Case, Review of the Literature and Review of Forty-Eight Cases of Purpura at University Hospital, Baltimore, Ann. Int. Med. **19**:799, 1943.

433. Rhodes, A. W., and Borelli, F. J.: Giant Hemangio-Endothelioma with Thrombocytopenic Purpura: Results of Roentgen Therapy, Am. J. Roentgenol. **52**:323, 1944.

434. Greco, A. J., and Ziedman, I.: Purpura as a Complication of Malaria. M. Bull. Vet. Admin. **20**:457, 1944.

fever and the purpura. Although severe purpura is considered an indication for interruption of therapeutic malaria, it is suggested by these authors that further study be undertaken to determine whether such patients can tolerate malaria at later dates.

The effect of splenic irradiation on increased vascular erythropermeability in purpura was studied by Madison, Squire and Morton [435] in 16 cases of purpura, entirely unselected for presence or absence of coexisting defects of coagulation. Splenic irradiation was given in doses of 50 to 200 r, with voltage of 140 peak kilovolts and filter of 0.25 mm. of copper every second or third day for three to five doses. All patients were kept under observation for "a considerable period," and changes in the blood vessels and the blood were frequently checked. Thirteen patients showed moderate to pronounced reversal of the vascular lesion, whereas 3 showed minimal or no response. In analysis, the authors concluded that in those patients whose conditions responded to roentgen therapy the lesions were essentially benign and reversible, many allergic in origin, and that in those whose conditions failed to respond the lesions represented purpura secondary to leukemia. It is suggested that irradiation may be a valuable measure in stopping spontaneous vascular leakage in selected cases of purpura, whether or not failure to respond to splenic irradiation strongly points to purpura secondary to progressive or malignant disease.

A special group of purpuras associated with infection is recognized under the name, Waterhouse-Friderichsen syndrome. According to Bush and Bailey,[436] Voelcker in 1894 was the first to describe the symptom complex of a fulminating febrile illness with purpuric eruption and bilateral adrenal hemorrhages. Waterhouse reported a case in 1911 and Friderichsen in 1918. The syndrome, subsequently called Waterhouse-Friderichsen, was for many years considered universally fatal, and Motsay and Crispell [437] state that of the 125 cases reported up to October 1943 90 per cent had been of children under 9 years of age. Of interest, therefore, are the recent reports of the syndrome in adult patients and of recovery. Although there are no pathognomonic or even uniform hematologic changes, the syndrome is considered here because of the prominence of the purpuric manifestations.

435. Madison, F. W.; Squire, T. L., and Morton, S. A.: Effect of Splenic Irradiation on Increased Vascular Erythropermeability in Purpura, J. A. M. A. **124**:735 (March 11) 1944. Madison, F. W.: Present Status of Hemorrhagic Diseases, Wisconsin M. J. **43**:688, 1944.

436. Bush, F. W., and Bailey, F. R.: Treatment of Meningococcus Infections with Especial Reference to Waterhouse-Friderichsen Syndrome, Ann. Int. Med. **20**:619, 1944.

437. Motsay, D. S., and Crispell, K. R.: The Waterhouse-Friderichsen Syndrome: Acute Bilateral Adrenal Hemorrhage, Guthrie Clin. Bull. **13**:140, 1944.

A general summary of the clinical picture of the syndrome is presented by Kasich and Disick,[438] together with detailed clinical and pathologic observations in 2 cases of young men aged 18 and 21 years. These authors believe the cause of hemorrhage into the adrenal glands is overwhelming toxemia, since it has been demonstrated that purpuric reactions can be produced in animals by injection of bacterial autolysates. Since the adrenal glands are among the most vascular organs in the body, it is postulated that the same factors producing purpura may also cause the adrenal hemorrhage. They consider the basis of the bleeding tendency from two aspects: (1) changes in the number of platelets in the circulating blood and toxic depression of the bone marrow and (2) injury to the capillary endothelium.

Thomas and Leiphart[439] report 2 cases of Waterhouse-Friderichsen syndrome in adults and consider in detail the role played by the adrenal glands. They reject destruction of the adrenal glands by hemorrhage as the cause of rapid death in the syndrome, which they believe is due to overwhelming sepsis and toxemia. They point out that of patients whose deaths are characterized by the same clinical features the clinician is unable to predict which will and which will not be found to have adrenal hemorrhages at autopsy and that, whereas adrenalectomized dogs may live for days, patients with Waterhouse-Friderichsen syndrome usually die within a matter of hours.

Bush and Bailey[436] present in detail 6 typical cases of Waterhouse-Friderichsen syndrome in 2 of which the patients recovered and in 4 of which they died. In the 4 fatal cases, 3 of the patients had bilateral and 1 had unilateral adrenal hemorrhage. Therapy in all instances consisted of intramuscular administration of desoxycorticosterone and adrenal extract, intravenous injections of sulfadiazine, meningococcus antitoxin, fluids and whole blood and oxygen inhalations, necessary to combat cyanosis and anoxemia.

Another patient with the syndrome who was successfully treated by a similar regimen is reported by Potter and Bronstein.[440] They believe that plasma is of especial value in combating shock, since the danger of

438. Kasich, M., and Disick, S.: Meningococcemia with Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome): Report of Two Cases. J. Tennessee M. A. **36**:464, 1943.

439. Thomas, H. B., and Leiphart, C. D.: Septicemia and Purpura with Adrenal Hemorrhage in the Adult (Waterhouse-Friderichsen Syndrome): A Discussion of the Role Played by the Adrenal Gland in the Production of the Syndrome; Report of Two Adult Cases, J. A. M. A. **125**:884 (July 29) 1944.

440. Potter, H. W., and Bronstein, L. H.: The Waterhouse-Friderichsen Syndrome: Report of a Case Terminating in Recovery, J. Lab. & Clin. Med. **29**:703, 1944.

cubic millimeter and profuse bleeding into the skin and from the gums and hematuria. The illness terminated fatally despite several blood transfusions. Necropsy showed the usual changes of such a purpura. Reference is made to a publication of Bamforth and Elkington,[447] in which 4 cases were reported and 19 cases were collected from the literature, of which 10 were fatal. They also refer to the publications of Scarborough and Stewart [448] and Scarborough and Horne,[449] in which it is claimed that vitamin P (hesperidin) is of value in the treatment of purpura occurring as a manifestation of poisoning with arsenic and bismuth in the treatment of syphilis.

Hemophilia.—Hemophilia has received little consideration in the recent literature. No new criteria for diagnosis have been established, nor have any new therapeutic measures been introduced. Kocar [450] has studied marrow material obtained by sternal puncture from persons with hemophilia, and reports that the megakaryocytes are increased and have either multilobed nuclei or multiple nuclei and that involution forms are rare. The red blood cells are frequently polychromatophilic, and an increase in lymphocytes is seen, but no diagnostic abnormalities could be noted.

The blood platelets in patients with hemophilia have been studied extensively in the past, but in most of the reports it has generally been considered that they carry out their mission in the coagulation process as individual agents rather than as agents linked in conjunction with the other formed elements of the blood. Assuming from the knowledge now available that in order for blood to clot a sudden and massive disintegration of platelets is necessary, Pennell [451] describes a conjunction phenomenon between platelets and red cells, which he regards as a mechanism by which the platelets can employ the surfaces of the red cell for the contact necessary to carry out mass disintegration of platelets. Since platelets of hemophiliac patients have been shown to be normal in various ways, it is suggested that red cells of hemophiliac persons may be responsible for diminished red cell—platelet conjugation in the disease. Pennell found the phenomenon to be decidedly reduced in

447. Bamforth, J., and Elkington, J. St. G.: Arsenobenzol Purpura, with Short Description of Four Cases, Quart. J. Med. **24**:381, 1931.

448. Scarborough, H., and Stewart, C. P.: Effect of Hesperidin (Vitamin P) on Capillary Fragility, Lancet **2**:610, 1938.

449. Scarborough, H., and Horne, G.: Capillary Resistance in ·Toxic Manifestation of Antisyphilitic Therapy, Lancet **2**:66, 1940.

450. Kocar, J.: Ueber die Sternalpunktion bei Hämophilie, Folia haemat. **67**:325, 1943.

451. Pennell, S.: A Platelet-Red Cell Conjugation Phenomenon and Its Relation to Blood Coagulation, Am. J. M. Sc. **205**:562, 1943.

patients with hemophilia and relatively increased in patients with thrombopenic purpura.

Feissly [452] suggests that in hemophiliac patients the serum albumin may play some role in the defective clotting mechanism.

Reports of cases of hemophilia by Echterracht [453] include an unusual instance of pseudotumor of bone (tibia) in a 13 year old child with hemophilia, with a description of clinical and roentgenologic features and of observations at autopsy. The tibial mass was thought by the orthopedist to represent hemangioma of the bone, osteomyelitis or osteogenic sarcoma, and by the roentgenologist, sarcoma of the tibia. The pathologic finding was a multilocular cavity occupied by a mass of deep red, jelly-like clotted blood forming the "tumor."

The management of hemophiliac patients continues to present a major problem. Many agents have been recommended for their treatment. With the exception of transfusions of blood and plasma, none have stood the test of time. The advent of the blood bank has made this type of treatment easily available, and it would now seem feasible to employ transfusions prophylactically rather than to restrict their use to emergencies. Munro and Jones,[454] in 1943, reported on a patient who apparently became refractory to ·repeated prophylactic transfusions. Poncher,[455] on the other hand, advocates their use in an attempt to keep the coagulation time as close to normal as possible and reports no untoward results with this type of management. Ratkovits [456] reports gratifying results in the treatment of a single patient with the oral and intramuscular administration of fresh raw mother's milk, which is said to contain a thermolabile zymoplastic substance. Such therapy has apparently been used for many years as part of the folklore of continental Europe.

It is known that suitable quantities of trypsin will reduce to normal, in vitro, the prolonged clotting time of hemophiliac blood. Tagnon [457] demonstrated a significant although transitory shortening of the coagulation time following intravenous injection of trypsin in 2 of 3 hemophiliac

452. Feissly, R.: Nouvelles etudes sur l'hemophilie; role des albumines plasmatiques dans la formation de la thrombine, Helvet. med. acta **11**:177, 1944.

453. Echterracht, A. P.: Pseudotumor of Bone in Hemophilia, Radiology **41**:565, 1943.

454. Munro, F. L., and Jones, H. W.: Detrimental Effect of Frequent Transfusions in Treatment of Patients with Hemophilia, Am. J. M. Sc. **206**:710, 1943.

455. Poncher, H. G.: Diseases of Blood in Infants and Young Children, Including the Hemorrhagic States, J. Pediat. **23**:680, 1943.

456. Ratkovits, H.: Zur Behandlung der Hämophilia, Wien. med. Wchnschr. **56**:728 1943.

457. Tagnon, H. J.: Effect of Intravenous Injection of Trypsin on the Blood Coagulation Time in Hemophilia, Proc. Soc. Exper. Biol. & Med. **57**:45, 1944.

persons. The effectiveness of such treatment did not compare with that of transfusion of blood or plasma, and the toxicity of trypsin by the intravenous route is so great that extreme caution must be observed in its use.

Hereditary Hemorrhagic Telangiectasia.—A review of the literature dealing with hereditary hemorrhagic telangiectasia from 1933 to 1944 is presented by Stock,[458] and 7 new cases are added. The possible relation between Osler's disease and other diseases, due not only to possible mesenchymal dysplasia but also to associated ectodermal dysplasia, is pointed out. Stock notes that in about 20 per cent of the recorded cases there is probably a total absence of a family history. Whether the patients in these cases can transmit the disease to their progeny is not known. The third recorded instance in the past eleven years in which the disease can be traced through six generations in one family is presented. The extreme rarity of this occurrence and the fact that the disease has become progressively milder during the last two generations in this family suggest self limitation of the hereditary transmission of the disease.

Another comprehensive review of literature dealing with hereditary hemorrhagic telangiectasia, including the history of the entity, synonyms, symptoms, sites of bleeding, diagnosis, prognosis, pathology and treatment, is presented by Barrock.[459]

Campbell [460] reports a case of hereditary familial telangiectasia with epistaxis and migraine which had been present in a 23 year old man since the age of 14. There was bleeding from the nose once each week, which was invariably preceded by typical migraine lasting half an hour to five hours, with relief after spontaneous epistaxis. The case is of special interest in that the nasal bleeding occurred in relation to the vasodilatation accompanying migraine. The family history showed that other members were affected by telangiectasia, but no statement is made as to other instances of migraine in the family.

Another interesting patient with hereditary familial telangiectasia is reported on by Wolfsohn.[461] There was a scarcity of telangiectasia in the skin, but an abundance of them in the mucous membrane of the upper part of the gastrointestinal tract, observed by gastroscopic examination. There were repeated hematemeses over a period of twelve

458. Stock, M. F.: Hereditary Hemorrhagic Telangiectasia (Osler's Disease): A Review of the Literature and Report of Cases, Arch. Otolaryng. **40**:108 (Aug.) 1944.

459. Barrock, J. J.: Hereditary Hemorrhagic Telangiectasia: Report of Case with Review of Literature, Wisconsin M. J. **43**:805, 1944.

460. Campbell, A. M. G.: Hereditary Familial Telangiectasis with Epistaxis and Migraine, Lancet **2**:502, 1944.

461. Wolfsohn, H.: Hereditary Familial Telangiectasis, Lancet **2**:581, 1944.

years, culminating fatally when the patient was 57. Such hereditary hemorrhagic telangiectasis in older persons is considered by Cutler [462] to exist in three forms: (1) an asymptomatic form, (2) a form characterized by mild bleeding amenable to local measures, such as radium cautery and cotton packs, helped by precautionary use of liquid petrolatum for crusts and (3) a form characterized by severe exsanguinating epistaxis, seen usually in persons in the age group of 45 to 60 in whom vascular changes play a prominent part and in whom the mortality is 4 per cent. The author considers repeated transfusions as mandatory and radium of variable and questionable value in treatment of the last form.

The Role of Vitamins in Coagulation of the Blood.—The part played by vitamins other than vitamin K in regard to bleeding has received but little attention during the past year. In an investigation of the mechanism responsible for the spontaneous hemorrhage caused by hypervitaminosis A, Light, Alscher and Frey [463] found overdosage of vitamin A to cause hypoprothrombinemia. In rats the effect of this overdosage can be controlled by simultaneous administration of a preparation of vitamin K (2-methyl-3-phytyl-1,4-naphthoquinone). However, there is no evidence that vitamin K is effective in preventing any of the other symptoms of toxicity occasioned by hypervitaminosis A, nor is it understood whereby vitamin K counteracts vitamin A in its production of hypoprothrombinemia.

In view of clinical reports on alteration of vascular permeability, or fragility, by various citrus products, a method was developed by Majovski and others [464] which can be used to show the protective action of certain peel fractions (vitamin P) in controlling vascular fragility. When air is suddenly evacuated from a jar in which mice are placed, hemorrhage occurs into the lungs of these mice. Crude hesperidin obtained from oranges and a water-soluble extract of lemon peel afforded protection to mice against this hemorrhage for a period of two to four hours after their administration. Pure hesperidin had little or no protective effect, but during the first two hours after its administration a greater degree of hemorrhage was apparent.

Having previously noted that total or partial depletion of vitamin C in guinea pigs produced no change in the prothrombin level and that

462. Cutler, M. H.: Hereditary Hemorrhagic Telangiectasia, Arch. Otolaryng. **40**:428 (Nov.) 1944.

463. Light, R. F.; Alscher, R. P., and Frey, C. N.: Vitamin A Toxicity and Hypoprothrombinemia, Science **100**:225, 1944.

464. Majovski, G. J., and others: Vascular Fragility and Permeability as Influenced by Various Agents: Description of Experimental Method and of Effects of Various Substances Related to Vitamin P, J. Pharmacol. & Exper. Therap. **80**:1, 1944.

high intakes of *l*-ascorbic acid did not affect the prothrombin time, Sullivan, Gangstad and Link [465] studied the effect of vitamin C on the fibrinogen content of plasma of normal and scorbutic guinea pigs and observed that with the onset of scurvy the fibrinogen increased noticeably. Restoration of normal fibrinogen levels occurred within two weeks after the addition of vitamin C to the basal diet.

Hemorrhagic Disease of the Newborn.—Further investigations dealing with the prothrombin status of the newborn continue to be reported. Both Pray [466] and Litchfield [467] confirm the observations of others that the administration of menadione to expectant mothers, either during the latter part of pregnancy or during labor, results in approximately normal prothrombin values in the infants and virtually eliminates the prolongation of the prothrombin times which usually occurs in the babies of untreated mothers between the second and fourth days of life. On funduscopic examination, Pray found notably fewer retinal hemorrhages among infants born of mothers treated before the onset of labor than among infants born of mothers treated only after labor had begun.

Hauser [468] is in accord with the opinion that treatment of the expectant mother is a better type of prophylaxis than is neonatal treatment of the child. He observed many hemorrhagic deaths despite neonatal therapy with vitamin K preparations. No authors report toxic deaths from large doses of vitamin K preparations.

Still an unexplained phenomenon is the fact that formula feedings during the first few weeks of life tend to counteract the usual neonatal hypoprothrombinemia. Pray [466] rejects as an explanation the hypothesis that by artificial feedings optimal conditions for the bacterial synthesis of vitamin K in the intestines are afforded. He was unable to demonstrate that administration of sulfaguanidine in full doses, beginning twelve hours after birth, had any inhibitory effect on the correction of the prothrombin time..

Mills, Cottingham and Mills [469] report that severe and fatal vitamin K deficiency can be produced in rats adapted to tropical heat by using vitamin K–free synthetic diets containing 0.5 per cent sulfaguanidine. At temperate coolness the manifestations are mild. The clinical

465 Sullivan, W. R.; Gangstad, E. O., and Link, K. P.: Note on Plasma Fibrinogen in Guinea Pig Scurvy, J. Biol. Chem. **152**:367, 1944.

466. Pray, L. G.: Hemorrhagic Disease of the Newborn: Prevention and Treatment with Vitamin K, Journal-Lancet **64**:1, 1944.

467. Litchfield, H. R.,. and others: Treatment of Prothrombinopenia with Water-Soluble Menadione, Am. J. Obst. & Gynec. **47**:642, 1944.

468. Hauser, F.: Vitamin K Prophylaxe bei 2520 Neugeborenen, Schweiz. med. Wchnschr. **73**:518, 1943.

469. Mills, C. A.; Cottingham, E., and Mills, M.: Environmental Temperature and Vitamin K Deficiency, Am. J. Physiol. **141**:359, 1944.

corollary of this is the finding that vitamin K deficiency is four times more prevalent among babies born in the Gulf States than among those born in the northern states.

Observations at some variance with these are reported by Lehmann,[470] who studied physiologic hypoprothrombinemia in 90 newborn infants through the first week of life. He found that babies born in the spring more commonly showed low values than those born in the summer. Admitting the difficulty of determining the level at which bleeding will occur, he nevertheless calculated that one third of the infants born in the summer and two thirds of those born in the spring would tend to bleed excessively if their vessels were damaged. He found that a 0.5 mg. dose of vitamin K analogue (sodium-2-methyl-1, 4-naphthohydroquinone disulfate) was as effective as a 5 mg. dose, whether given by mouth or intramuscularly. He points out that the factor determining the speed of increase in prothrombin is the reactive power of the liver, not the time taken for the vitamin to be absorbed.

Hardwicke [471] found the minimal effective daily dose of Synkavite (tetra sodium-2-methyl-1, 4-naphthohydroquinone) in the prevention of neonatal hypoprothrombinemia to lie somewhere between 0.005 and 0.0005 mg. Approximately 0.5 mg. of the test substance will apparently lower the excessively high prothrombin time and maintain it within normal range without further medication. No alteration in prothrombin time could be attributed to the administration to the mothers of several of the more common barbiturates.

Anticoagulant Therapy; Dicoumarin and Heparin. Vitamin K Preparations.—The successful use of heparin or dicoumarin in the prevention and treatment of thrombotic accidents is largely responsible for the current clinical interest in the anticoagulants. Beyond stating that the chemists are in agreement as to the synthesis and structural requirements for dicoumarin activity and that 3, 3'-methylene-bis (4-hydroxydicoumarin) is considered the most potent anticoagulant of the 4 hydroxycoumarin class,[472] no attempt will be made to review the extensive biochemical literature dealing with the anticoagulants.

470. Lehmann, J.: Vitamin K as Prophylactic in 13,000 Infants, Lancet **1**:493, 1944.

471. Hardwicke, S. H.: Studies on the Minimal Effective Dose of a Water-Soluble Vitamin K Substitute in the Prevention of Hypoprothrombinemia in the Newborn Infant, J. Pediat. **24**:259, 1944.

472. Overman, R. S., and others: Studies on Hemorrhagic Sweet Clover Disease: Anticoagulant Activity and Structure in 4-Hydroxy-Coumarin Group, J. Biol. Chem. **153**:5, 1944. Rocha e Silva, M.: Estudos sobre a dicoumarina-3,3'-metilenobis-(4-hidroxicoumarina); historico e experiencias preliminares, Arq. Inst. biol., São Paulo **14**:293, 1943.

The modes of action of these agents are considered by Dyckerhoff [473] and by Douthwaite.[474] Dyckerhoff believes that dicoumarin exerts its anticoagulant effect in the first phase of clotting through incapacitating thrombokinase and that it does not enter into the second phase of clotting. Douthwaite holds to the more commonly accepted theory that dicoumarin exerts a specific action in the reduction of the prothrombin content of the blood while heparin acts by retarding conversion of prothrombin to thrombin.

Dicoumarin therapy in thrombotic emergencies is discussed in two papers by Evans.[475] The more detailed report is based on the observation of 46 patients treated over an eighteen month period. All received dicoumarin; 36 received supplementary heparin for the first two to five days (the latent period before which dicoumarin had not effectively lowered the prothrombin time), and 6 had paravertebral sympathetic block as well as dicoumarin. Hemorrhagic phenomena were evident eight times, but of 2 deaths, only 1 could unequivocally be attributed to dicoumarin. The contraindications to dicoumarin therapy are listed as hepatic damage, an already lowered prothrombin time or hemorrhagic diathesis. The necessity of a daily estimation of prothrombin time is emphasized. In this series pulmonary embolism occurred only once and was not fatal. The second paper is concerned with 55 patients considered as having potential pulmonary embolism, who were successfully treated with dicoumarin and heparin.

Barker [476] reports on the use of dicoumarin postoperatively for 624 patients at Mayo Clinic. One hundred and eleven patients had had pulmonary embolism or infarction and survived. In only 2 patients in this group did subsequent thrombosis occur, and in both of these the author feels the prothrombin time was not adequately elevated. Dicoumarin was given to 83 patients with postoperative thrombophlebitis. Further thrombophlebitis developed in 2 patients, but in none did embolism occur. Thrombosis or embolism did not occur in a group of 259 patients who had had abdominal hysterectomies and received, postoperatively, dicoumarin prophylactically. Dicoumarin was given prophylactically to 141 patients with such disorders as anemia, varicose

473. Dyckerhoff, H.: Ueber den Reaktionsmechanismus der Hemming der Blutgerinnung durch 33'-Methylen-di-(4-hydroxy-cumarin) genannt AP. Biochem. Ztschr. **316**:397, 1944.

474. Douthwaite, A. H.: Spoiled Sweet Clover and Other Anticoagulants, Guy's Hosp. Gaz. **58**:91, 1944.

475. Evans, J. A.: (*a*) Dicumarol Therapy in Thrombotic Emergencies, New England J. Med. **230**:131, 1944; (*b*) Anticoagulation Therapy of Postoperative Venous Thrombosis and Pulmonary Embolism. S. Clin. North America **24**:534, 1944.

476. Barker, N. W.: The Use of Dicumarol in Surgery, Collect. Papers Mayo Clin. **35**:414, 1944.

veins and obesity, because it was felt there was increased risk of post-operative thrombosis and embolism, and to 30 patients who with previous operations had had thrombophlebitis or pulmonary embolism. In no instance in these two groups did thrombosis or embolism occur. On the basis of this experience, Barker feels that adequate elevation of prothrombin time by the administration of dicoumarin is almost com-pletely effective in the prevention of postoperative thrombosis and pulmonary embolism.

Gefter, Kramer and Reinhold [477] reported on a series of 34 patients with thromboembolic disease at the Philadelphia General Hospital who were treated with dicoumarin. Twenty-seven recovered, and 7 died. No changes attributable to dicoumarin were noted in the leukocyte count, hemoglobin content, blood sugar and urea nitrogen values, van den Bergh icterus index, retention of sulfobromophthalein or specific gravity, sugar or formed elements in the urine. No increase in antithrombin or decrease in platelets was observed. The only observed alteration was a decrease in prothrombin which, after a latent period, was reduced to levels of 25 to 30 per cent of normal in two days, with gradual rise to ± 50 per cent of normal in four weeks, despite continued therapy. The clotting time was uniformly increased. Bleeding times were vari-able and, except in 1 instance, within normal limits.

The only toxic manifestation observed by Gefter, Kramer and Rein-hold was a hemorrhagic tendency. Withdrawal of the drug resulted in prompt recovery in 4 of the 5 patients with bleeding. The fifth required a transfusion of whole blood.

Thill and his associates [478] report a definite reduction in the inci-dence of formation of thrombi after the injection of a sclerosing agent, monoethanolamine oleate, in dogs prepared with dicoumarin in doses equivalent to therapeutic doses administered to human beings.

Davis and Porter [479] treated 43 patients with postpartum throm-bosis with dicoumarin. Although the conditions varied so widely in severity that to find an exact parallel series for comparison was impos-sible, dicoumarin was believed to effect a slight but definite amelioration of pain and to be followed by a fairly rapid diminution in edema, with shortening of the average stay in the hospital. In all instances the drug was well tolerated. Of special interest was the lowering of the incidence of pulmonary embolism from 9 per cent to 4 per cent. These authors

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477. Gefter, W. I.; Kramer, D. W., and Reinhold, J. G.: Clinical Experience with Dicumarol, Am. Heart J. **28**:321, 1944.

478. Thill, C. J., and others: Hemorrhagic Agent 3,3′-Methylenebis (4-Hydroxycoumarin): Its Effect in Prevention of Experimental Thrombosis, Proc. Soc. Exper. Biol. & Med. **54**:333, 1943.

479. Davis, A., and Porter, M.: Dicoumarin in the Treatment of Puerperal Thrombosis, Brit. M. J. **1**:718, 1944.

feel that dicoumarin therapy is of unequivocal value, at least in treatment of the type of patient on which they made their investigations. Eckstrom [480] believes that dicoumarin is generally of real value in preventing the extension of intravascular thrombosis.

Bollman [481] is in accord with this clinical observation despite the fact that experimentally he could find no evidence that dicoumarin or heparin modifies infarction or enhances the blood supply of the tissue after the blood vessels supplying the part have been occluded.

Essentially similar programs for dicoumarin dosage are outlined by Evans,[475a] Gefter, Kramer and Reinhold,[477] Eckstrom [480] and Bingham, Meyer and Howard.[482] An initial dose of 300 mg. is given, followed on the next day by 200 mg. with a subsequent daily dose of 0 to 200 mg., depending on the prothrombin time, which all authors agree must be determined daily. Allowance must be made for a latent period of twenty-four to seventy-two hours. The therapeutic level is reached when the prothrombin content of the blood is 25 to 50 per cent of normal.

Bingham, Meyer and Howard observed that the administration of dicoumarin may be safely combined with administration of heparin when prompt prolongation in the coagulation time is desired. With lengthening of the prothrombin time, evidence of the effectiveness of dicoumarin, the heparin may be discontinued.

Walker and Rhoads [483] found that only one half to one third the amount of heparin required to produce a given effect in the non-coumarinized person is needed to produce the same effect in the coumarized person, thus allowing, by means of intramuscular injection of heparin, a prolonged evenly maintained increase in blood coagulation time with avoidance of the inconvenience of continuous intravenous medication.

Bryson and Code [484] observed prolongation of the anticoagulant action of heparin given intramuscularly by suspension in beeswax-oil mixture, both in animals and in human beings. A distinct elevation in clotting time was consistently produced, which was demonstrable

480. Eckstrom, E. E.: The Clinical Use of Dicumarol: Report of Cases, Minnesota Med. **27**:455, 1944.

481. Bollman, J. L.: Failure of Dicumarol and Heparin to Modify Experimental Renal Infarction, Proc. Staff Meet., Mayo Clin. **19**:248, 1944.

482. Bingham, J. B.; Meyer, O. O., and Howard, B.: Studies on the Hemorrhagic Agent 3,3' Methylenebis (4-Hydroxycoumarin): A Report on Further Clinical Observations, Am. J. M. Sc. **205**:587, 1943.

483. Walker, J., and Rhoads, J. E.: Effect of Dicumarol on Susceptibility to Action of Heparin, Surgery **15**:859, 1944.

484. Bryson, J. C., and Code, C. F.: Prolonged Anticoagulant Action of Heparin in Beeswax Mixture, Proc. Staff Meet., Mayo Clin. **19**:100, 1944.

at four hours, reached its peak at twenty-four hours and persisted for three to five days.

· Opinion is at variance as to the proper management of bleeding as a complication of overdosage with dicoumarin. Transfusion is favored by Jeanneret [485] as the only effective method of controlling the hemorrhage of overdosage with dicoumarin. In his experience therapy with a vitamin K preparation was equivocal, but 30 mg. was the largest dose of the vitamin K preparation he employed. With single 64 mg. doses (menadione bisulfite) Cromer and Barker [486] obtained satisfactory reduction in the prothrombin time of such patients, and transfusion was not necessary.

From another approach. Shapiro [487] has indicated the efficacy of vitamin K in controlling this type of bleeding. He was interested in the observation of Link and his associates that the quantitative degradation products of dicoumarin yielded 2 mols of salicylic acid and that in rats hypoprothrombinemia could be produced by salicylates and prevented by vitamin K. Shapiro therefore studied the course of 17 adult patients who were receiving salicylic acid in doses of 5 to 6 Gm. daily for the effect of the salicylate on the prothrombin time. Determinations of prothrombin time were done before and after supplementary doses of menadione in doses of 2 to 9 mg. daily. Before menadione was given, 13 patients displayed prolonged prothrombin times after three to five days of salicylate therapy. Menadione was protective. Since there are no fixed levels at which hypoprothrombinemia causes bleeding, Shapiro advises serial determinations of prothrombin time for patients receiving salicylate therapy. He feels that 1 mg. of menadione should be given prophylactically for each gram of acetylsalicylic acid. Complicating factors, such as fever, toxemia and limited nutrition, may make such adjuvants as ascorbic acid necessary.

A more potent vitamin K preparation for such therapeusis may be available soon. Mikhlin [488] reports the isolation from maize stigmas of an antihemorrhagic factor, for which he suggests the designation "vitamin K_3." This substance is effective in decreasing the prothrombin time not only in vitamin K–deficient subjects but in normal persons

485. Jeanneret, H.: Contribution à l'étude de l'action anticoagulante de la dicoumarine synthetique sur l'organisme humain, Schweiz. med. Wchnschr. **74**: 696, 1944.

486. Cromer, H. E., Jr., and Barker, N. W.: The Effect of Large Doses of Menadione Bisulfite (Synthetic Vitamin K) on Excessive Hypoprothrombinemia Induced by Dicumarol, Proc. Staff Meet., Mayo Clin. **19**:217, 1944.

487. Shapiro, S.: Studies on Prothrombin: The Effect of Synthetic Vitamin K on the Prothrombinopenia Induced by Salicylate in Man, J. A. M. A. **125**:545 (June 24) 1944; correction, ibid. **125**:923 (July 29) 1944.

488. Mikhlin, D. M.: Characteristics of Antihemorrhagic Factor from Maize Stigmata (Vitamin K₃), Biokhimiya **8**:158, 1943.

as well. It effects an acceleration of coagulation time to two to three times as fast as normal, coincident with a rise in prothrombin level by as much as 75 per cent.

Shlevin and Lederer [489] had an opportunity to study the histopathologic features in an instance of uncontrollable bleeding due to dicoumarin in which transfusion was of only temporary value. The features observed at necropsy were extreme engorgement of all the blood vessels, particularly the capillaries, arterioles and venules and a mild degree of cirrhosis of the liver. Whether the latter contributed to the toxicity of the dicoumarin is not known. McCarter, Bingham and Meyer [490] undertook to determine whether or not the liver was damaged by the use of dicoumarin. Large doses of dicoumarin were given to dogs, which were then killed. On histopathologic study there was found definite evidence of serious damage to small blood vessels, with disseminated gross and microscopic hemorrhages, and prominent swelling of the renal glomeruli, but no consistent lesions of the liver attributable to dicoumarin and no necrosis of the liver were found in any of the 29 dogs studied.

Quick [407] states that aside from depressing prothrombin, which is synthesized in the liver, dicoumarin appears to exert no deleterious effect on the liver.

The existence of a relation between hypoprothrombinemia and clinical hepatic disease is well recognized. Esculies [491] reviews the current knowledge concerning coagulation of blood with special emphasis on the role of vitamin K and the common sources of vitamin K deficiency. Although insufficient intake of vitamin K is rare because of the synthesis carried on by the intestinal flora, it may occur and is easily corrected by administration of vitamin K preparations. Deficient absorption of vitamin K and hepatic insufficiency are cited by Esculies as the two common sources of vitamin K deficiency. Kaufman [492] emphasizes the necessity of a healthy liver in the utilization of vitamin K.

No definite relation between the degree or duration of jaundice and the prothrombin level of the blood or the percentage of excretion of hippuric acid in patients with disease of the biliary tract could be demonstrated by Sinha.[493] He points out that in disease of the biliary

489. Shlevin, E. L., and Lederer, M.: Uncontrollable Hemorrhage After Dicoumarol Therapy with Autopsy Findings, Ann. Int. Med. **21**:332, 1944.

490. McCarter, J. C.; Bingham, J. B., and Meyer, O. O.: Studies on the Hemorrhagic Agent 3,3' Methylenebis (4-Hydroxycoumarin) : IV. The Pathologic Findings After the Administration of Dicumarol, Am. J. Path. **20**:651, 1944.

491. Esculies, J.: Coagulation sanguinea, Rev. san. mil., Asunción **139**:221, 1943.

492. Kaufman, J.: Prothrombin Studies, McGill M. J. **11**:74, 1941.

493. Sinha, S. K.: Significance of Blood Prothrombin Value in Diseases of Biliary Tract, J. Indiana M. A. **13**:67, 1943.

tract hypoprothrombinemia may be due to either of two factors: (1) a deficiency in the absorption of vitamin K, which can be corrected by either bile salts or a synthetic preparation of vitamin K (Kapilin), and/or (2) damage to the hepatic cells caused by pressure from the dilated intrahepatic biliary channels, the hypoprothrombinemia due to which is not correctable either with bile salts or with a vitamin K preparation.

Because of the apparent failure of severely damaged livers to respond to treatment with vitamin K preparations, Kinsey [494] attempted to prepare blood donors for such patients with large doses of menadione. The prothrombin content of the blood of such donors did not change with the administration of menadione. The benefit derived by the patient from such specially prepared donors was no different from that derived from unprepared donors.

The use of vitamin K preparations in other hemorrhagic situations has been investigated. Gubner and Ungerleider [495] report gratifying results in the control of menorrhagia not due to local pelvic abnormalities by administration of a synthetic naphthoquinone with pronounced vitamin K-like activity (Synkvite). Its beneficial effect is thought to be due to its action on prothrombin formation, since the latter is a sensitive index of hepatic integrity and since there is evidence that hepatic function is impaired at the onset of menstruation.

Farber and Miller [496] confirm previous reports of prothrombin deficiencies in tuberculous patients. Such deficiencies are most pronounced in bleeding patients but do not parallel the amount of blood loss and are definitely present in patients with constitutional symptoms. Thirty-three per cent of nonbleeding tuberculous patients and 58 per cent of the bleeding tuberculous patients studied had prothrombin deficiencies. Synthetic vitamin K restored the plasma prothrombin concentration of these patients but had no effect on their hemorrhages. Such instances of prothrombin deficiency are regarded simply as manifestations of a general nutritional deficiency.

Sharp, Wolter and Vonder Heide [497] present data based on the study of the prothrombin concentration and bleeding and clotting times for cutaneous blood of 221 patients with common blood dyscrasias.

494. Kinsey, R. E.: A New Aid in Control of Hemorrhage in Severe Damage to the Liver: Transfusions of Blood Fortified by Administration of Vitamin K to Donors, Arch. Int. Med. **73**:131 (Feb.) 1944.

495. Gubner, R., and Ungerleider, H. E.: Vitamin K Therapy in Menorrhagia, Indust. Med. **13**:301, 1944.

496. Farber, J. E., and Miller, D. K.: Nutritional Studies in Tuberculosis: Prothrombin Deficiency and Vitamin K, Am. Rev. Tuberc. **48**:406, 1943.

497. Sharp, E. A.; Wolter, J. G., and Vonder Heide, E. C.: Prothrombin in Disorders of the Blood, Am. J. Clin. Path. **14**:44, 1944.

Their data suggest that prothrombin deficiency of moderate severity may be present in the active phases of the common blood disorders, as may be abnormal bleeding from the cutaneous capillaries. No direct correlation could be established between the decreased prothrombin times and prolonged bleeding times, but the authors suggest that further study is indicated.

CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION

The changes in the peripheral blood that accompany infection have long been recognized. It is emphasized, however, by many authors that serial determinations of the white cell count, particulary differential counts, are of infinitely more value in following the course of an illness than is any single set of determinations. The value of the hemogram in the interpretation of a variety of infections has been restated by several investigators.

In studying 62 cases of recurrent sore throat, Schilling and Jonssen [498] found repeated hemograms of value in differentiating allergic conditions from bacterial infections and so in choosing between medical and surgical management. Whereas those with bacterial infections showed the usual neutrophilic, monocytic and lymphocytic phases associated with infection, about half of the patients showed early lymphocytosis and high easinophilia, which were interpreted as indicating allergy. Relapses and complications tended to follow premonitory changes in the hemogram. Metke [499] considers that the hemogram is of value in determining the severity and development of complications in diphtheria. Serial white cell counts and differential counts for patients with pelvic inflammatory disease have been reappraised by Umbricht,[500] with the conclusion that, alone, such information is neither diagnostic nor prognostic but that, when correlated with clinical data, it may be a valuable aid in the proper management of the patient.

De Barros [501] accepts the concept of three stages portrayed by the hemogram during an infectious process: (1) a neutrophilic, or "fighting," phase; (2) a monocytic, or defensive, phase involving lymphocytoid, monocytoid or endotheloid cells of the reticuloendothelial system and (3) a lymphocytic, or recovering, phase. He notes that

498. Schilling, V., and Jonssen, K.: Angina als periodisch rezidvierende Infektion nach den Ergebnissen der biologischen Leukocyten-kurve, Folia haemat. **68**:4, 1944.

499. Metke, H.: Ueber die biologische Leukocyten-Kurve bei der Diphtherie, Folia haemat. **68**:72, 1944.

500. Umbricht, W.: Das weisse Blutbild bei entzündlichen gynäkologischen Erkrankungen, Schweiz. med. Wchnschr. **73**:719, 1943.

501. de Barros, N. V.: Estudo do hemograma emgeral; sua aplicação no puerpério normal e infectado, Folia clin. et biol. **13**:142, 1941.

in infections of the puerperium these changes are accompanied by a variable degree of anemia and a tendency toward an increase in platelets and suggests that the latter may account for the frequent association of thrombophlebitis. By means of the injection of blocking substances, he has been able to demonstrate hyperactivity of the reticuloendothelial system during pregnancy and postulates that this activity may explain the hyperbilirubinemia of pregnancy.

Luz and Siede [502] studied the blood picture in cases of epidemic hepatitis and found that at the onset there is a leukocytosis as in other infectious diseases. At first the entire leukocyte picture is affected, but with the onset of jaundice the count returns toward normal, later falling to subnormal values. These three phases are associated, respectively, with neutrophilic, lymphocytic and monocytic blood pictures. Highly characteristic of the disease is the appearance during the second phase of plasma cells of lymphoid origin. In the marrow an increase in myelopoiesis, such as is to be found in other infections, was observed.

Orens, Kelley and Agress [503] had the opportunity to study 43 patients with atypical pneumonia within a period of six weeks and were impressed not only by the constancy of the hematologic features but by the ways in which they differed from those in patients with bacterial pneumonias. During the first ten days the white blood cell count was normal or slightly below normal. Although the lymphocytes were unchanged or even slightly increased in number, the neutrophils showed some "shift to the left." Coincident with amelioration of the general symptoms and resolution of the pulmonic process, there occurred a variable leukocytosis associated with relative or absolute lymphocytosis. Frequently lymphocytes with morphologic changes similar to those seen in cases of infectious mononucleosis were observed. It is emphasized that the late development of leukocytosis is not an indication of relapse or complication and that for the patient with a history of recent infection of the respiratory tract showing an abnormal blood picture roentgenograms of the chest may be necessary to make the diagnosis of atypical pneumonia..

Further studies on the leukocytosis-promoting factor are reported by Menkin.[504] Whereas leukotoxine is said to be concerned only with local migration or diapedesis of polymorphonuclear leukocytes and so fails to alter the number of circulating leukocytes when introduced into the circulation, a leukocytosis-promoting factor can be

502. Luz, K., and Siede, W.: Das Blutbild der Hepatitis epidemica, Deutsche Ztschr. f. Verdauungskr. **7**:67, 1943.

503. Orens, M. H.; Kelley, R. W., and Agress, H.: Abnormal Blood Picture of Atypical Pneumonia, M. Bull. North African Theat. Op. **2**:56, 1944.

504. Menkin, V.: Further Studies on the Leukocytosis-Promoting Factor and on Necrosin in Inflammatory Exudates, Am. J. M. Sc. **208**:290, 1944.

obtained from inflammatory exudates. After injection of this substance, there appears in the marrow an increase in granulocytic forms and megakaryocytes and in the peripheral blood an increase in immature and nonfilamentous granulocytes as well as in the total leukocyte count. The author suggests the possibility of using this factor therapeutically in correction of various sluggish conditions of the bone marrow.

The association of eosinophilia with a variety of unrelated disorders is still not well understood. Its frequent occurrence in persons with schistosomiasis, ascariasis or hydatid infections is confirmed by Porrier,[505] who failed, however, to find any eosinophilia among 15 patients with amebic dysentery. Allen [506] has observed that in persons with hookworm infections eosinophilia may precede by two to six weeks the demonstration of ova in the stools. A case of chronic ulcerative colitis with eosinophilia of 51 per cent is reported by Stickney and Heck.[507] Burkhart and Montgomery [508] could find no correlation between eosinophilia of tissue and of blood in a variety of dermatoses. Schilling, Rothe and Zimmer [509] consider early eosinophilia important in the recognition of sporadic cases of scarlet fever. Stickney and Heck encountered the highest degree of eosinophilia in patients with allergic disorders, such as hay fever and asthma. However, among 418 patients with high grade eosinophilia no instances of pulmonary eosinophilic infiltration (Loeffler's syndrome) were observed. Pirkle and Davin [510] report eosinophilia of 33 per cent (total white blood cell count 8,800) in a 54 year old woman with migrating pneumonitis of eight months' duration. The patient had no signs of bronchial asthma. Schlecht [511] offers further evidence that Loeffler's syndrome is allergic in origin, comparing the histopathologic features with those observed in sensitized guinea pigs.

Of particular interest are the recent case reports following Weingarten's description in 1943 of an apparently new disease entity which

505. Porrier, M.: Considerations sur l'éosinophilie dans les maladies paracitaires, Bull. Soc. path. exot. **37**:59, 1944.

506. Allen, H. C.: Eosinophilia in the South Pacific, U. S. Nav. M. Bull. **42**:1241, 1944.

507. Stickney, J. M., and Heck, F. J.: The Clinical Occurrence of Eosinophilia, M. Clin. North America **28**:915, 1944.

508. Burkhart, R. J., and Montgomery, H.: Tissue Eosinophilia: Its Significance in Various Dermatoses, Proc. Staff Meet., Mayo Clin. **19**:38, 1944.

509. Schilling, V.; Rothe, I., and Zimmer, G.: Scharlach als in Schuken ablaufeude Infektion nach der biologischen Leukocytenkurve, Folia haemat. **68**:19, 1944.

510. Pirkle, H. B., and Davin, J. R.: Loeffler's Syndrome; Transient Pulmonary Infiltrations with Blood Eosinophilia, Am. Rev. Tuberc. **50**:48, 1944.

511. Schlecht, H.: Das allergische, eosinophile Lungeninfiltrat, Deutsche med. Wchnschr. **70**:189, 1944.

he thought to be peculiar to certain parts of India, characterized by severe spasmodic bronchitis, malaise, leukocytosis and high eosinophilia. The cause is unknown, but it is not believed to be an allergic state. The response to arsenic is phenomenal, with disappearance of the constitutional and pulmonary symptoms and subsidence of the eosinophilia. Increases in all manifestations following the initial injections of neoarsphenamine have been described, after which dramatic cures ensue. Parsons-Smith [512] reports from Egypt an instance of this so-called tropical eosinophilia in a 28 year old English airman. The maximum leukocyte value and eosinophil percentage were 20,000 per cubic millimeter and 34 per cent, respectively. The clinical course and response to neoarsphenamine were typical.

Shah [513] reported the case of a 22 year old Hindu man with fever, malaise and cough. Rales and rhonchi were present throughout the lungs, and there was roentgenographic evidence of peribronchial infiltration. The white blood cell count was 19,000 per cubic millimeter, and the eosinophils were 70 per cent. The symptoms promptly subsided after injections of diethylamine oxyacetylaminophenylarsonate (acetylarsen), although mild eosinophilia persisted.

Another instance of febrile pulmonary disease associated with leukocytosis and extreme eosinophilia which responded promptly to treatment with an organic arsenic compound is reported by Chakravarty and Roy.[514] Emerson [515] reports a case wherein all the signs and symptoms of the tropical eosinophilia coincident with severe intercurrent infection appeared eight months after the patient returned to the United States from India. Carbarsone therapy effected the complete disappearance of all evidence of eosinophilia.

RELATION OF THE THYROID GLAND TO HEMOPOIESIS

Because of conflicting reports regarding the changes in hemopoiesis in patients with thyroid dysfunction, Wilson [516] undertook a study of the blood and bone marrow of a series of 31 patients suffering from severe thyrotoxicosis and of 1 patient suffering from myxedema. The changes in the blood and bone marrow and other changes produced in rats by thyroidectomy and by the injection of thyroxin were also investigated. The 31 untreated thyrotoxic patients showed mild

512. Parsons-Smith, B. G.: Tropical Eosinophilia, Lancet **1**:433, 1944.

513. Shah, R. L.: A Case of Pseudo-Tuberculosis of the Lungs with Eosinophilia, Indian M. Gaz. **78**:597, 1943.

514. Chakravarty, U. N., and Roy, S. C.: A Case of Tropical Eosinophilia? Indian M. Gaz. **78**:596, 1943.

515. Emerson, K., Jr.: Tropical Eosinophilia, U. S. Nav. M. Bull. **42**:118, 1944.

516. Wilson, T. E.: The Thyroid Gland and Haemopoiesis, M. J. Australia **1**:261, 1944.

anemia and increased cellularity of the marrow affecting all the cells except the monocytes. The increased cellularity of the marrow was not reflected in the peripheral blood. Examinations of blood and bone marrow repeated two to three weeks after thyroidectomy on 10 patients showed no significant changes. The single patient with myxedema studied showed mild anemia and decreased cellularity of the marrow. In rats transformed into cretins by thyroidectomy mild anemia and hypocellularity of the marrow developed, whereas adult thyroidectomized rats had normal blood values and rats injected with thyroxin showed increased cellularity of the marrow. The author reviews the various explanations of the role of the thyroid in hemopoiesis and concludes that the thyroid gland exercises a nonspecific control over the metabolism of the elements of the marrow, resulting in their hyperplasia in thyrotoxicosis and in their hypoplasia in cretinism and myxedema.

You, Kwang and Chu [517] studied the effects of thyroidectomy and thyroid feeding in rabbits. Thyroidectomized animals showed, up to the fifth week, a progressive fall in the hemoglobin content and red blood cell count, associated with increased erythrocyte fragility and reticulocytosis. Subsequently their values were stabilized, with significantly lower red blood cell counts and hemoglobin values. There was, however, a slight decrease in the number of reticulocytes, and a slight decrease in fragility of the red cells. The finding of reticulocytosis associated with increased red cell fragility in thyroidectomized animals and of the reverse in thyroid-fed animals suggested to the authors that the thyroid hormone may exert a protective action on erythrocytes, which would otherwise be subject to more rapid destruction.

That endocrine glands other than the thyroid may exert some control over hemopoiesis is suggested by the report of Armstrong.[518] His patient, a middle-aged woman, had severe, long-standing myxedema associated with anemia. For five years large doses of thyroid had been given daily without correction of the anemia. The administration of testosterone propionate with desiccated thyroid was followed by subjective and hematologic improvement.

METHODS AND MISCELLANEOUS MATERIAL

Much attention has recently been directed toward standardization of various hematologic laboratory procedures. King, Gilchrist and Delory [519] are among those who have attempted to evaluate the accuracy

517. You, S. S.; Kwang, D. R., and Chu, J. P.: The Influence of the Thyroid Gland on the Blood Picture in the Rabbit, Proc. Chinese Physiol. Soc. **2**:50, 1944.

518. Armstrong, C. D.: Case of Myxedema with Ascites, Anemia, Myxedema Heart, Angina and Delayed Relaxation of Reflexes, with Note on Therapeutic Effects of Testosterone Propionate, Stanford M. Bull. **2**:25, 1944.

519. King, E. J.; Gilchrist, M., and Delory, G. E.: Accuracy of Haemoglobin Methods, Lancet **1**:239, 1944.

of the current methods of determination of hemoglobin content. They found that the least satisfactory methods were those which depend on matching a standard by dilution, such as the Haldane and Sahli procedures. The photoelectric and photometric methods possessed high degrees of accuracy. The cyanmethemoglobin procedure was the most accurate method tested and is recommended by these authors for research purposes. Although it is simple and easy, the hazard involved in the routine use of cyanide is recognized and must be considered before the method is accepted for general clinical use. The alkaline hematin and carboxyhemoglobin methods were slightly less accurate but are considered satisfactory for most purposes. King and his associates give the technics of these various procedures. Horecker and Brackett [520] report a spectrophotometric method for the simultaneous determination of methemoglobin. carbonylhemoglobin and total hemoglobin, said to be accurate to within about 1 per cent. The performance of the method with the Coleman Spectrophotometer is described. The details of the photoelectric method for routine estimates of hemoglobin content are outlined by Reeve,[521] together with an analysis of the common sources of error. The copper sulfate method of Phillips and van Slyke for determining the specific gravity of blood has been adapted to determinations of hemoglobin content, with an accuracy reputedly within 2 per cent of the value as determined by oxygen-carrying capacity.

Duffie [522] describes a plungerless, one cup colorimeter in which a green filter incorporated in the eyepiece absorbs red. The instrument is designed for reading hemoglobin values as well as for many chemical determinations on the blood; it is small, simply constructed and easily adjusted, as well as accurate.

Attempts in the past to determine red blood cell counts other than by direct enumeration have not met with much success. However, Parker, Spicer and Porter [523] present a method for computing the red cell count on the photoelectric colorimeter. Satisfactory correlation with hemocytometer values are offered for 25 patients. Caution is expressed in reference to accepting colorimeter readings if obvious microcytosis or macrocytosis is observed when examining the stained

520. Horecker, B. L., and Brackett, F. S.: A Rapid Spectrophotometric Method for the Determination of Methemoglobin and Carbonylhemoglobin in Blood, J. Biol. Chem. **152:**669, 1944.

521. Reeve, E. B.: Observations on Photo-Electric Estimation of Total Haemoglobin, J. Path. & Bact. **56:**95, 1944.

522. Duffie, D. H.: Hemoglobin Estimation by Revolutionary Colorimetric Method of Kennedy, with Further Report on Simple Instrument for Facilitating Utilization of Principle, J. A. M. A. **126:**95 (Sept. 9) 1944.

523. Parker, G. M.; Spicer, H. E., and Porter, H.: Method for Computing Red Cell Count on Photoelectric Colorimeter, Am. J. Clin. Path. **8:**37, 1944.

film. The authors, however, consider the method simple and rapid and suitable for routine counts.

Further observations are reported by Mallery and Randolph [524] on the use of a diluting fluid for white blood cells consisting of 0.1 per cent eosin and 0.1 per cent methylene blue (methylthionine chloride) dissolved in equal parts of propylene glycol and water for simultaneous white blood cell counts and counting chamber differential counts. For general purposes the results are said to compare favorably with those obtained with the use of standard acetic acid diluting fluid and Wright-stained cover slip films.

The usual multiple tube method of determining erythrocyte fragility with macroscopic reading is criticized by Fennel [525] for its well known inconvenience and obvious dependency on the personal equation in interpretation. A simple one tube method for "screening" of patients with abnormal fragility is outlined, together with the technic of a more elaborate serial dilution method, using pipetted amounts of blood instead of drops and the photocolorimeter for reading, thereby eliminating the personal equation. Fennel states that decreased erythrocyte fragility is more common than increased fragility.

Hegglin and Maier [526] outline a specific test for the recognition of Marchiafava's syndrome based on the concept that the "heat resistance" of the erythrocytes of patients with this disease is less than normal, so that in the presence of complement hemolysis takes place and the degree of hemolysis increases as the temperature rises.

Success in the staining of sections of bone marrow with Giemsa stain is reported by Lewis, [527] who suggests that the method should work equally well on marrow films. The technic is given. Arnold [528] describes a method of preparing and staining bone marrow films with equal parts of Wright's and Leishman's stains or with Jenner-Giemsa or May Grunwald-Giemsa stains. The need for meticulously clean glassware and great technical care is emphasized.

A simple method of venipuncture is outlined by Markuson [529] whereby the blood is drawn into a vial in which mild negative pressure

524. Mallery, O. T., Jr., and Randolph, T. G.: The Effect in Vitro of Propylene Glycol on Leucocytes, J. Lab. & Clin. Med. **29**:203, 1944.

525. Fennel, E. A.: Erythrocyte Fragility, Am. J. Clin. Path. **8**:21, 1944.

526. Hegglin, R., and Maier, C.: "Heat Resistance" of Erythrocytes: Specific Test for Recognition of Marchiafava's Anemia, Am. J. M. Sc. **207**:624, 1944.

527. Lewis, E. J.: Giemsa Stain for Bone and Bone Marrow Sections, Canad. J. Med. **6**:5, 1944.

528. Arnold, G. M.: A Method of Preparing and Staining Bone Marrow Smears, Canad. J. Med. **6**:47, 1944.

529. Markuson, K. E.: A New Technique in Drawing Blood for Serodiagnostic Tests: Use of the Hemospast, J. Indiana M. A. **37**:400, 1944

has been produced. The details for preparation of the necessary equipment are given. The method obviates the obvious handicaps in the common syringe-needle method of aspiration, requires no special skill and is advocated for mass testing. The name given to this device is the "hemospast."

The difficulty frequently encountered in giving fluids, electrolytes or blood intravenously to young or debilitated patients has led to a search for some other method of introducing these substances into the circulation. Turkel and Bethell [530] offer a solution to this problem in the description of a new and simple instrument for the administration of such fluids through the bone marrow. It may be used for sternal infusions in treatment of adults and older children and in the treatment of younger children for intratibial infusions. Arbeiter and Greengard [531] report on the successful use of infusions in tibial bone marrow in treatment of 34 young children, using primarily the needle described by Turkel. Meola [532] considers infusions in marrow of inestimable value because of the ease and expediency with which they are done. The indications, fluids used and ages and conditions of the patients for 326 such infusions are recorded. Parada [533] also reports favorably on the use of intramedullary transfusion in children, giving details of his technic.

Although the blood sedimentation test was not introduced to medical practice until 1921, it had been observed by physicians for many centuries that there was an increased plasma layer in blood "drawn" for many conditions having little in common save fever. Despite its lack of specificity, as an auxiliary method in diagnosis much importance is attached to this simple procedure. In a series of 270 patients, 146 of whom were tuberculous, Crowe [534] found the sedimentation rate in 69 per cent paralleled the presence or absence of pulmonary disease, as determined by other criteria. Cimmino [535] found increased sedi-

530. Turkel, H., and Bethell, F. H.: A New and Simple Instrument for Administration of Fluids Through Bone Marrow, War Med. **5**:222 (April) 1944.

531. Arbeiter, H. J., and Greengard, J.: Tibial Bone Marrow Infusions in Infancy, J. Pediat. **25**:1, 1944.

532. Meola, F.: Bone Marrow Infusions as a Routine Procedure in Children, J. Pediat. **25**:13, 1944.

533. Parada, L. S.: Transfusión de sangre en los niños por vía intramedular osea, Pediat. Américas **2**:249, 1944.

534. Crowe, M.: The Blood Sedimentation Test in a Tuberculosis Dispensary, Irish J. M. Sc., 1944, p. 531.

535. Cimmino, V.: Studio sulla velocita di sedimentazione in Eritrea; la V. di S. nella tuberculosi pulmonare e nella lues, Boll. Soc. ital. di med. e ig. trop. **2**:55, 1943; Studio sulla velocita di sedimentazione in Eritrea; la velocita di sedimentazione nella febbre ricorrento, ibid. **2**:76, 1943; Studio sulla velocita di sedimentazione in Eritrea; la V. di S. nel tifo esantematico, ibid. **2**:64, 1943.

mentation rates in patients with pulmonary tuberculosis and observed rapid rates not only in patients with untreated syphilis but also in those with syphilis resistant to treatment. He reports an increase in the sedimentation rate during the second week of illness with typhus, with a slow return to normal during convalescence. He observed no relation between the severity of the typhus, the intensity of the Weil-Felix reaction and the speed of sedimentation. In patients with relapsing fever an increase in the sedimentation rate occurred not only during episodes of fever but also during the apyrexic periods. Although specific therapy cures the relapsing fever, a long interval elapses before the sedimentation rate returns to normal. This the author attributes to the prolonged action of the arsenobenzene preparations used in the treatment of the disease. Mendel and Korenberg [536] report further observations in support of the maintenance of elevated sedimentation rates of blood removed from patients with cancer, Hodgkin's disease and leukemia in contrast to that observed in persons with nonmalignant pathologic conditions. He therefore advocates twenty-four hour observations of the sedimentation rates as a diagnostic adjunct. The sedimentation rates of 125 patients with poliomyelitis were studied by Dokow.[537] Sedimentation rates of 42 per cent of the patients were normal and of 58 per cent increased, and they never decreased. Great acceleration was rare. There was no correlation between the sedimentation rate and the extent of the clinical process.

Using both the Westergren macromethod and the Kato micro-method, McKinley and Jackson [538] found that the sedimentation test was of definite value in the evaluation of the clinical course of patients with rheumatic fever. The micromethod, avoiding venipuncture, was more convenient when the determinations were made by an experienced technician but was less reliable in examination of acutely ill patients. However, values obtained by either method paralleled satisfactorily the course of the disease process. A simple method of determining sedimentation rate involving the use of only 0.3 cc. of blood, which may be obtained from the finger tip, is outlined by Phillips.[539]

A new application of the sedimentation rate is offered from experience in the armed services. An epidemic of mumps among navy per-

536. Mendel, D. L., and Korenberg, M.: Maintenance of the Sedimentation Rate of Erythrocytes in Cases of Cancer, Hodgkin's Disease, and Leukemia, Canad. M. A. J. **51**:353, 1944.

537. Dokow, F.: Ueber Blutbild und Erythrocytensenkungsgeschwindigkeit bei Poliomyelitis acuta anterior, Inaug. Dissert., Med. Fak. **94**:1, 1937.

538. McKinley, J. B., and Jackson, R. L.: Comparison of Westergren and Kato Erythrocyte Sedimentation Rate Readings; Relation to the Clinical Status of Children with Rheumatic Fever, Am. J. Dis. Child. **67**:474 (June) 1944.

539. Phillips, E. C.: Sedimentation Rates, Pub. Health Nursing **36**:474, 1944.

sonnel enabled Candel and his associates [540] to study 37 cases, 13 uncomplicated, 10 complicated by meningitis and 14 complicated by orchitis. Study of the erythrocyte sedimentation rates showed no significant deviation from normal in cases of uncomplicated mumps or of mumps complicated by meningitis, but a decided increase in sedimentation rate occurred in patients with mumps complicated by orchitis. The rise in sedimentation rate may precede the appearance of orchitis and may persist for weeks after recovery, possibly denoting the persistence of an inflammatory or degenerative process in the testes.

It has been repeatedly observed, especially in treatment of infants with splenomegaly, that subcutaneous injections of epinephrine hydrochloride produce an outspoken increase in the number of circulating erythrocytes. These increases are usually associated with obvious shrinking of the spleen. Watson and Paine,[541] therefore, undertook to examine blood from both the splenic artery and the splenic vein, before and after injections of epinephrine, of 9 patients at the time of splenectomy for acquired and familial hemolytic icterus, chronic myeloid leukemia with associated mild hemolytic anemia and thrombocytopenic purpura. In general, splenic venous blood showed a great increase in erythrocyte concentration after injection of epinephrine into the artery. Associated with this was a decrease in mean corpuscular hemoglobin concentration and also an increase in fragility and spheroidicity. The exact cause of this decrease in hemoglobin concentration is unknown. It was thought that it might be due to an intracorpuscular degeneration of a fraction of the hemoglobin in the intact erythrocytes during the period of their sequestration in the spleen, analogous to that observed when significant increases of bilirubin and iron in the supernatant plasma occur after incubation of sterile blood for as little as six hours.

540. Candel, S.; Wheelock, M. C.; Turk, M. P., Jr., and Smoot, J. L.: Erythrocyte Sedimentation Rate in Mumps and Its Complications, U. S. Nav. M. Bull. **42:** 571, 1944.

541. Watson, C. J., and Paine, J. R.: A Study of the Splenic Venous Blood, with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes, Before and After Splenic Arterial Injection of Adrenalin, Am. J. M. Sc. **205:**493, 1943.

Book Reviews

Health Instruction Yearbook, 1945. Edited by O. E. Byrd, Ed.D., Associate Professor of Hygiene, School of Health, Stanford University. Price, $3. Pp. ix + 344. Stanford University, Calif.: Stanford University Press, 1945.

While browsing in his local public library this reviewer first encountered this volume. He liked its looks, the systematic way in which the contents were arranged, the index and the short digests of a large amount of literature. For the book discusses, in the form of abstracts, almost every paper pertaining to public health which was of interest during the past year.

He discovered that *The Journal of the American Medical Association* knew the series and had reviewed the two first volumes.

Of the first, *The Journal* said (**124**:131 [Jan.] 1944) that it was an interesting beginning: To be sure, such books had been written before and had been unsuccessful. Now, a recent upsurge of interest in public health and in health education perhaps offered this particular yearbook a propitious start; in any event, it commenced in an interesting and useful fashion.

Toward the second volume *The Journal* (**126**:799 [Nov.] 1944) was more gracious. By now the potential usefulness of such a yearbook was better established, especially since it continued to be edited with particularly good judgment. On the whole, *The Journal* said that the two volumes together constituted a valuable source of reference.

The ARCHIVES is glad to have met the third volume. We believe that the series should find a place in every medical library to which medical students have access and that many practicing physicians can learn much from it. Medical libraries unacquainted with the undertaking will do well to obtain copies of all the volumes so far in print; for, so long as present editorial standards are maintained, each subsequent volume will be worth shelving.

What People Are; A Study of Normal Young Men. By Clark W. Heath, M.D., and others. Price, $2. Pp. xvi + 141, with illustrations. Cambridge, Mass.: Harvard University Press, 1945.

Seven years ago an institution known as the Grant Study was established at Harvard University "to achieve a more thorough understanding of human behavior characteristics and to interpret them more precisely and wisely." The work began with a study of a selected group of young men in which not only their physical characteristics were analyzed but also their psychologic makeup, in order that they might receive advice concerning how best to pursue successful careers. This book gives the results of what has been accomplished so far.

It is an interesting compilation, combining physical and clinical measurements in common clinical use with more imponderable mental reactions and leading to the general conclusion that within every person, whether he is classified by some scheme as "normal" or not, lie the potentialities of better integration and better conduct of life.

The variations encountered in measuring healthy young men in such ways are interesting: the differences in appearance, for example, that are so obvious between a man with strong masculine makeup and one who has weak masculine components. The methods that were employed in measuring mental attributes are ingenious and will serve as a guide to future studies. On the whole, many physicians, and certainly all directors of health departments in schools and colleges, will find this short volume worthy of careful study. It is a stimulating and interesting bit of medical literature.

The Care of the Neurosurgical Patient. By Ernest Sachs, M.D.· Price, $6. Pp. 268, with 177 illustrations. St. Louis: C. V. Mosby Company, 1945.

The author of this book, as is well known, is a professor of neurologic surgery, an eminent writer and a skilled clinician. To read his book is a joyful experience because it contains so much good teaching and valuable clinical observations, and at the same time is so readable.

The preface states that it was prepared especially for house officers and for the young surgeons who are hoping to enter the specialty of neurosurgery. In reality, it is a text that will be appreciated fully as much by internists or radiologists, or even by pathologists. The care of the patient is discussed; diagnostic methods and preoperative and postoperative care are thoroughly described, and the problems which the expert neurosurgeon encounters most frequently are well analyzed.

The print is excellent; the illustrations—of which there are many—are apt and tend to clarify the text, and the bibliography is carefully selected for the reader who wishes more detailed knowledge. On the whole, here is a volume which, deservedly, is bound to achieve wide popularity.

Prescribing Occupational Therapy. Second Edition. By William Rush Dunton Jr., M.D. Price, $2.50. Pp. 151. Springfield, Ill.: Charles C Thomas, Publisher.

This well arranged little book could be read with advantage by every medical student and physician. After discussing the general philosophy of occupational therapy the author gives details of application for various categories of patients, such as medical, surgical, mental, orthopedic and cardiac. There is a bibliography after each chapter which brings the subject fully up to date. There is an index.

News and Comment

AMERICAN SOCIETY FOR RESEARCH IN PSYCHOSOMATIC PROBLEMS

The annual meeting of the American Society for Research in Psychosomatic Problems will be held at the Hotel Pennsylvania, New York, May 11 and 12, 1946. "Contributions of Military Medicine to Psychosomatic Medicine" will be discussed in the morning and "Psychosomatic Aspects of Orthopedic Practice" in the afternoon. After the annual dinner an illustrated parody on "New Advances in Psychosomatic Investigative Technic," by Dr. Bertram D. Lewin, will be presented. On May 12 there will be volunteered contributions.

Because of space limitation, reservations should be made at least two weeks prior to the meeting. Further information may be procured from Dr. Roy G. Hoskins, chairman, program committee, 714 Madison Avenue, New York 21.

CORRECTION

Attention has just been called to the fact that the name of one of the authors—Dr. Morgan Swirsky—was omitted from the article entitled "Extragenital Chorionepithelioma in the Male," which was published in the November-December issue of the ARCHIVES OF INTERNAL MEDICINE (**76**:347, 1945). The names of the authors there given were Hyman M. Chernoff, M.D.; Theodore S. Evans, M.D., and Charles J. Bartlett, M.D. Dr. Morgan Swirsky's name should be added to the names listed.

NONSUPPURATIVE POSTSTREPTOCOCCIC (RHEUMATIC) PNEUMONITIS

Pathologic Anatomy and Clinical Differentiation from Primary Atypical Pneumonia

COMMANDER CLYDE R. JENSEN (MC), U.S.N.R.

CLINICAL recognition of pulmonary lesions in rheumatic fever is increasing. Many careful descriptions of the pathologic anatomy of rheumatic pneumonitis, obtained from cases in which death was due to rheumatic carditis, have finally brought into focus what seems to be a highly characteristic picture, gross and microscopic, now generally familiar to pathologists. Pathologic details may not be so familiar to most clinicians. It is not yet possible, however, to identify the disease solely on the basis of a single anatomic change in the lungs alone—to recognize any one feature as pathognomonic. This is due somewhat to the fact that rheumatic fever is always a disease of many organs, and when only a part of the picture is viewed either clinically or anatomically in one organ at a time it seems to blend with other conditions, usually regarded as separate diseases.

So far as this concerns the pulmonary lesion, the pathologic picture found in rheumatic fever may easily be confused with that of other conditions, in particular with that found in primary virus infections of the respiratory tract. Clinical confusion also is likely. In order to explain this fact better, an unusual case is here selected for presentation in which death in the acute stage of rheumatic fever resulted primarily from the pulmonary lesions of this disease, unaccompanied with significant cardiac involvement. The pathologic changes in the lungs and kidneys will be given in detail, to be used as the basis for illustrating the general tissue lesions of rheumatic fever and for discussing the task of differentiating clinically between rheumatic penumonitis and conditions which it may simulate.

REPORT OF A CASE

Clinical History.—The patient was a 19 year old seaman. His past health had always been good except for numerous attacks of tonsillitis in childhood, with nothing to suggest rheumatic fever. The present illness began aboard ship on Dec. 21, 1944, with a typical attack of scarlet fever, observed by a medical officer. He seemed to recover promptly and returned to full duty in ten days. On Jan. 5, 1945, fifteen days after the onset of the pharyngitis of the scarlet fever, while otherwise well, he began to have pain in one hip. On January 10 severe pain and swelling appeared in both ankles also, along with tenderness in the muscles of the neck and slight shortness of breath. On January 12 he was transferred to a Naval hospital. At this time, aside from the slight shortness of breath and acute pain and swelling in the ankles, there were slight puffiness of the hands and face, numerous erythrocytes and casts in the urine and moderate albuminuria. With rest and heavy doses of sodium salicylate the symptoms referable to the joints receded in four days, but the slight generalized edema and shortness of breath continued. The blood pressure was 165 systolic and 105 diastolic. With an intake of fluid maintained between 2,000 and 3,000 cc. daily, the output of urine remained always over 1,000 cc. daily. The blood nonprotein nitrogen was 60 mg. per hundred cubic centimeters on admission, falling to 25 mg. just before death. Shortness of breath continued unchanged until January 18, when severe dyspnea and cyanosis began, and he had to be kept continually under oxygen during the remaining two days of life. Rales were audible throughout the lungs. Repeated physical examinations failed to show evidence of cardiac enlargement or murmurs, and the final electrocardiogram, three days before death, was normal. He died in great respiratory distress on Jan. 20, 1945, exactly thirty days after the onset of the acute pharyngitis and fifteen days after the first appearance of rheumatic pain.

Observations at Autopsy.—Gross: All organs were grossly as in health except the lungs, kidneys and spleen. The spleen was large, weighing 340 Gm., and was uniformly soft and purple. The kidneys were darker red than normal and contained many minute purple spots in the subcapsular surface; otherwise they were normal.

Lungs. Each pleural cavity was free of adhesions and contained only a small amount of thin fluid. The pleural surfaces were glistening except for a few small dull patches. Large bronchi contained much moderately thick dark red fluid; their mucosa was dark gray-red. The main divisions of the pulmonary artery were free of clots. The lungs together weighed 1,990 Gm. and were essentially alike. Peribronchial lymph nodes were large, soft and gray-black. The lung parenchyma throughout varied from red to dark plum-purple and was only slightly crepitant. The darker purple regions were not clearly demarcated and were irregularly distributed, and such regions particularly were rather solid but not hard, more resilient than friable. Only a small amount of thin, bloody fluid ran freely from the cut surface, but much could be expressed with pressure.

Microscopic: Lungs (fig. 1). In all sections the picture was essentially the same. Few alveoli contained air. Many of them were filled with homogeneous material characteristic of edema fluid, and most of them contained cells also. Many of the cells were large mononuclear cells of phagocytic type, some containing a few fine spots of brown pigment, but so-called heart failure cells, heavily

laden with brown pigment, were sparse. In some alveoli were desquamated chains of septal cells, mixed in places with amorphous debris. In many places there was a thick, eosinophilic hyaline membrane along the periphery of alveolar ducts, seemingly fixed as a lining to the wall, often partially surrounding an air pocket. In many places there were numerous erythrocytes free in the alveoli, indicating recent capillary hemorrhage, but in no place was this hemorrhage dense over a large area. Mononuclear cells predominated in the exudate. Mingled with them were varying numbers of polymorphonuclear leukocytes, usually sparse, nowhere
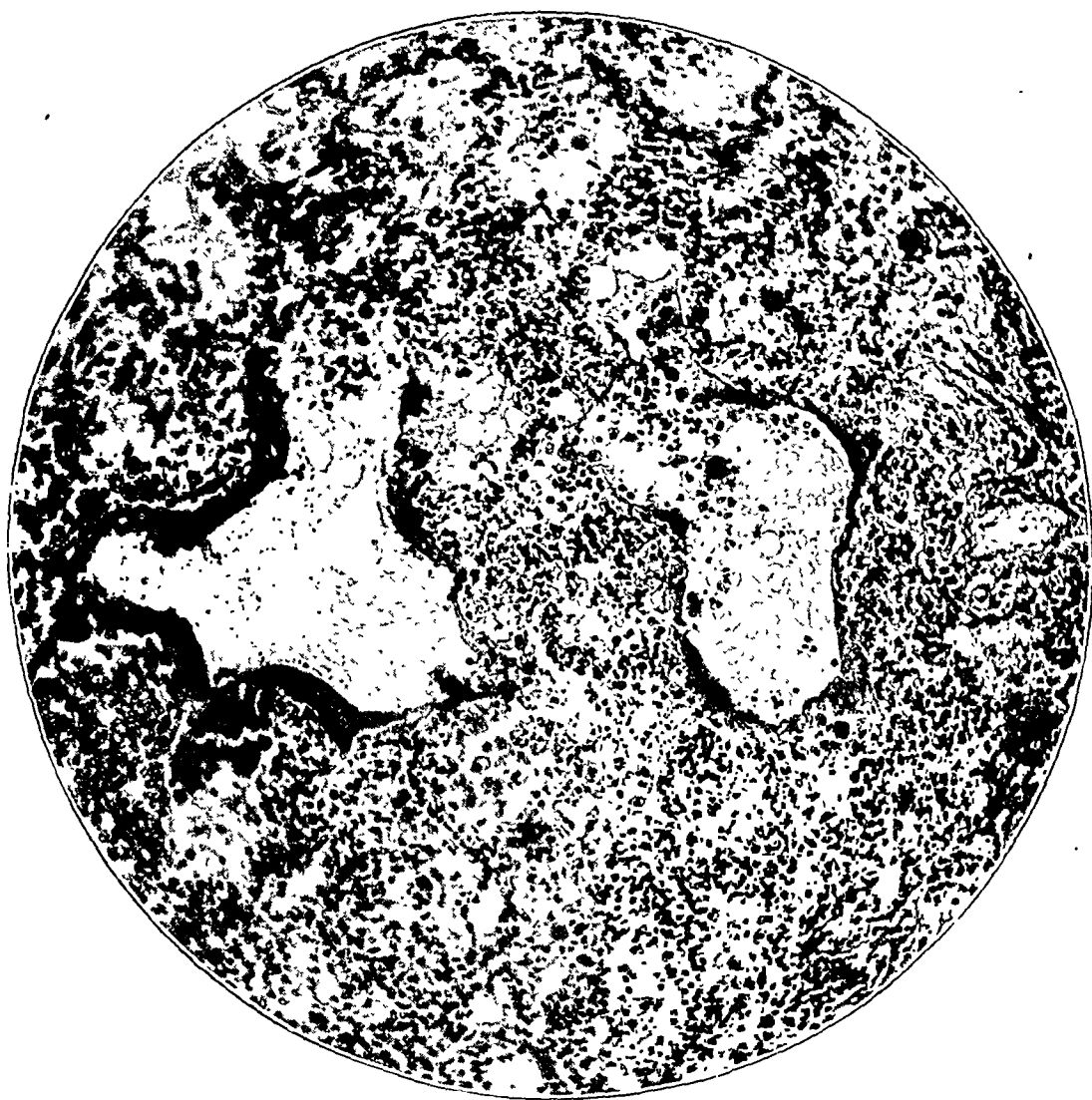
Fig. 1.—Lung. Engorgement of capillaries, exudation of mononuclear cells, edema and hyaline membrane partially lining two alveolar ducts. Low power (× 130).

heavy. Capillaries were engorged. Alveolar walls contained many mononuclear cells, some recognizable as lymphocytes and many as swollen endothelial or other large mononuclear cells. In some places there were small but dense collections of lymphocytes and plasma cells. There were strands of fibrinous material extending from some alveolar walls into the spaces. Interstitial edema was particularly noticeable in larger septums, and here also there were many focal infiltrations

of lymphocytes and plasma cells, sometimes with a few histiocytes and leukocytes. Although rarely a giant cell with hyperchromatic and irregular nucleus was encountered, nothing resembling a true Aschoff nodule was found. No organisms were identified with the MacCallum-Goodpasture stain.

Kidneys (fig. 2). About 15 per cent of the tubules were filled with blood. Others contained finely granular debris, and a few contained hyaline casts. There was little edema in the interstitial tissue generally, but there were many small regions of capillary hemorrhage, some with demonstrable rupture directly into a tubule (fig. 3). In such regions, disintegration of tubular epithelium was recog-
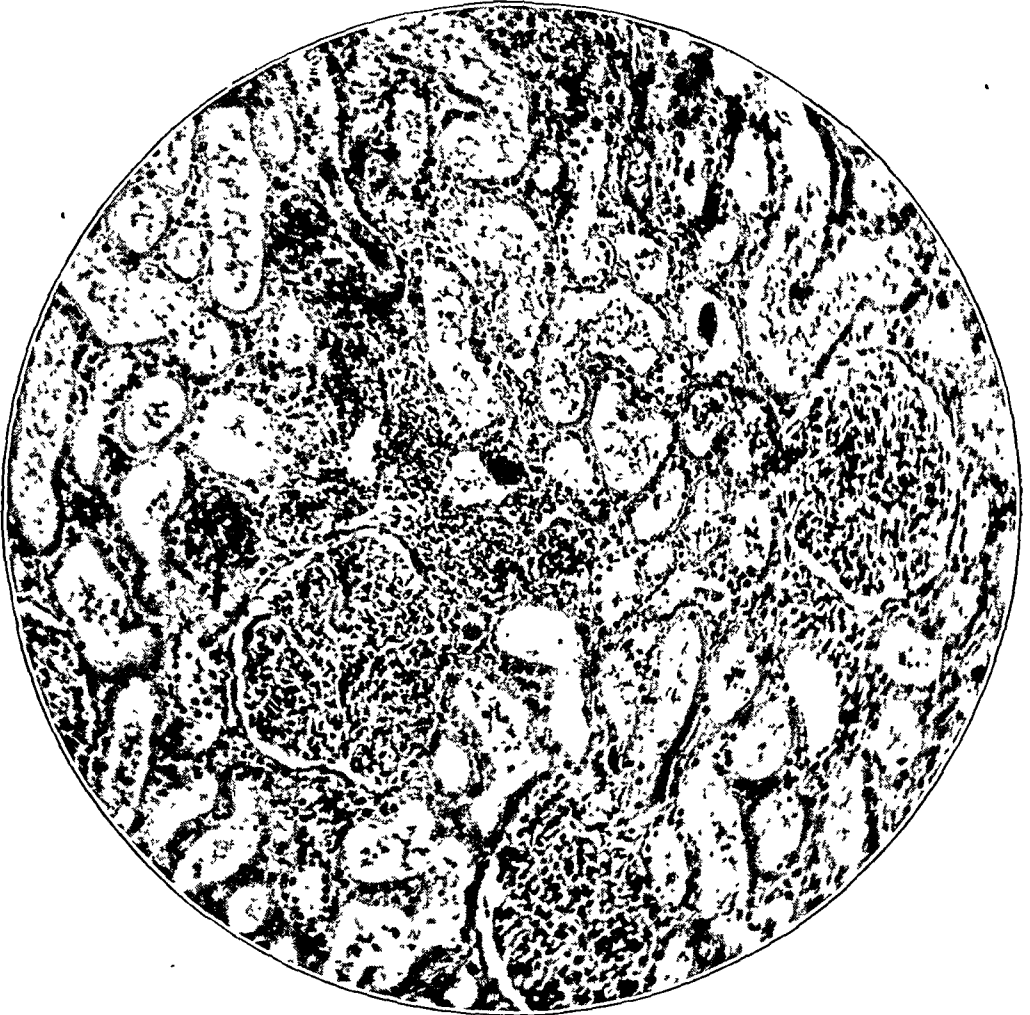
Fig. 2.—Kidney. Glomeruli relatively normal; blood cell casts in several tubules. Low power ($\times$ 130).

nizable, but tubular epithelium otherwise was normal throughout. There were other small regions in which there were focal collections of lymphocytes and plasma cells in the interstitial tissue (fig. 4). There was no hemorrhage in such regions, suggesting that they were older lesions than those of hemorrhage and might not have been preceded by actual hemorrhage. Some of these collections of cells were around small veins, and a few were subintimal in medium-sized veins, producing a bulge in the intima. Most of the glomeruli were rather bloodless, their capil-

lary channels collapsed and the nuclei still vesicular and perhaps slightly swollen but without proliferation. Rarely there were a few erythrocytes free in a glomerular space, in contrast to the relative profusion of blood in the tubules.

Heart. Under the pericardium and endocardium there were small collections of lymphocytes and plasma cells, about equal in numbers and in the pericardial fat these had a perivascular arrangement (fig. 5). There were rare plasma cells and lymphocytes in perivascular fibrous tissue in the myocardium but no dense cell collections here.
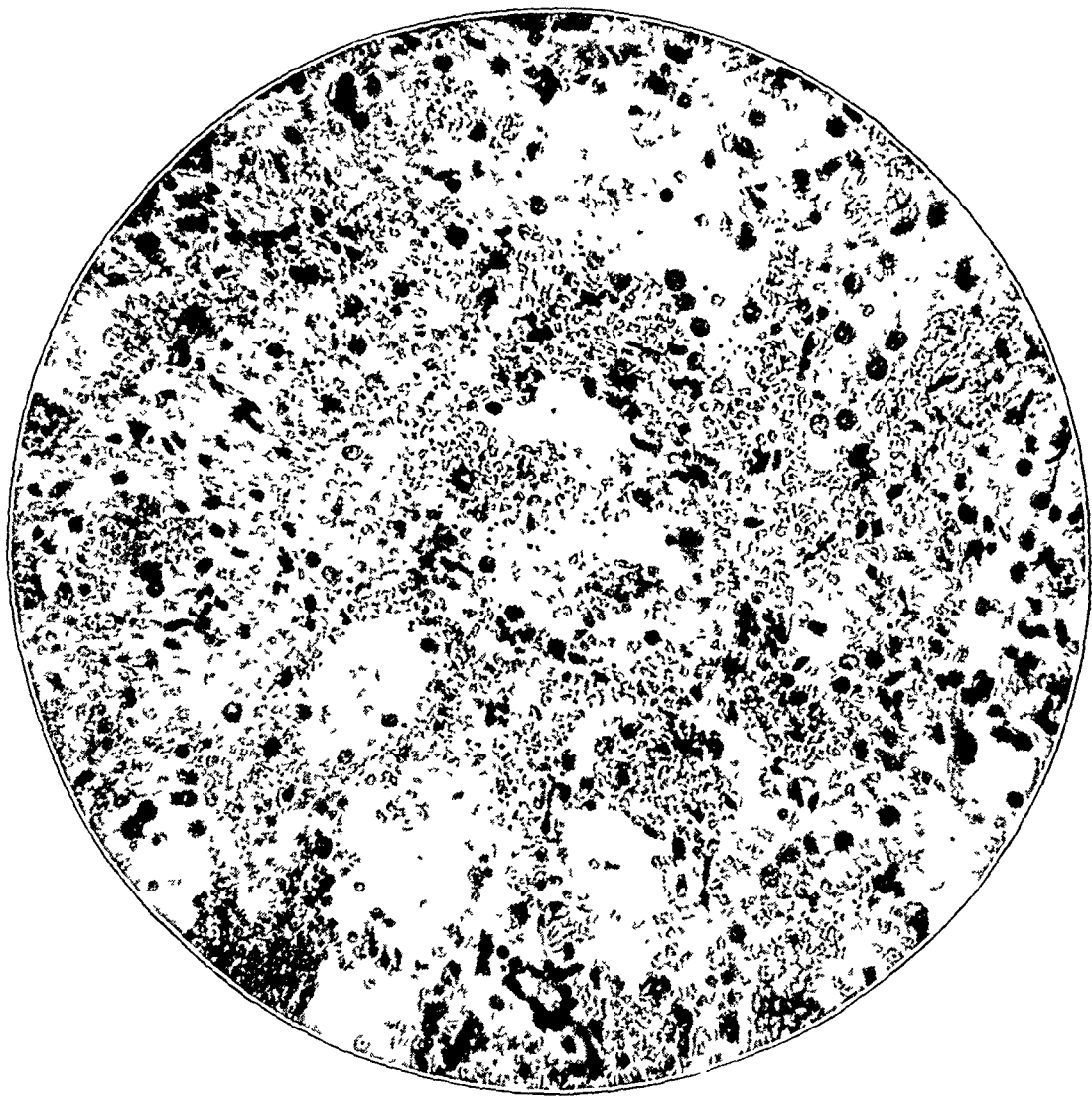
Fig. 3.—Kidney. Capillary hemorrhage with direct rupture into tubules. High power (× 380).

Other organs. In sections from the liver (fig. 6), pancreas, testicles, synovial tissue of the left ankle, suprarenal glands and spleen, there were small scattered collections of lymphocytes, sometimes with plasma cells, similar to those in the pericardium, but nowhere were the changes so prominent as in the lungs and kidneys. Of several sections from the brain, one from the hypothalamic region contained two small perivascular hemorrhages but no cell infiltrations.

Comment.—Cultures of the original throat infection were not made, but the fact that the patient had typical scarlet fever is enough evidence

that he was infected with a hemolytic streptococcus. He died in the postinvasive, nonsuppurative stage of this infection, having had concurrently three prominent sequels of such infection, acute hemorrhagic nephritis, acute arthritis and acute pneumonitis. At the time of death the articular symptoms had subsided. It is not unusual for such symptoms to subside sooner than those referable to other organs, possibly because joints are so easily put at complete rest.
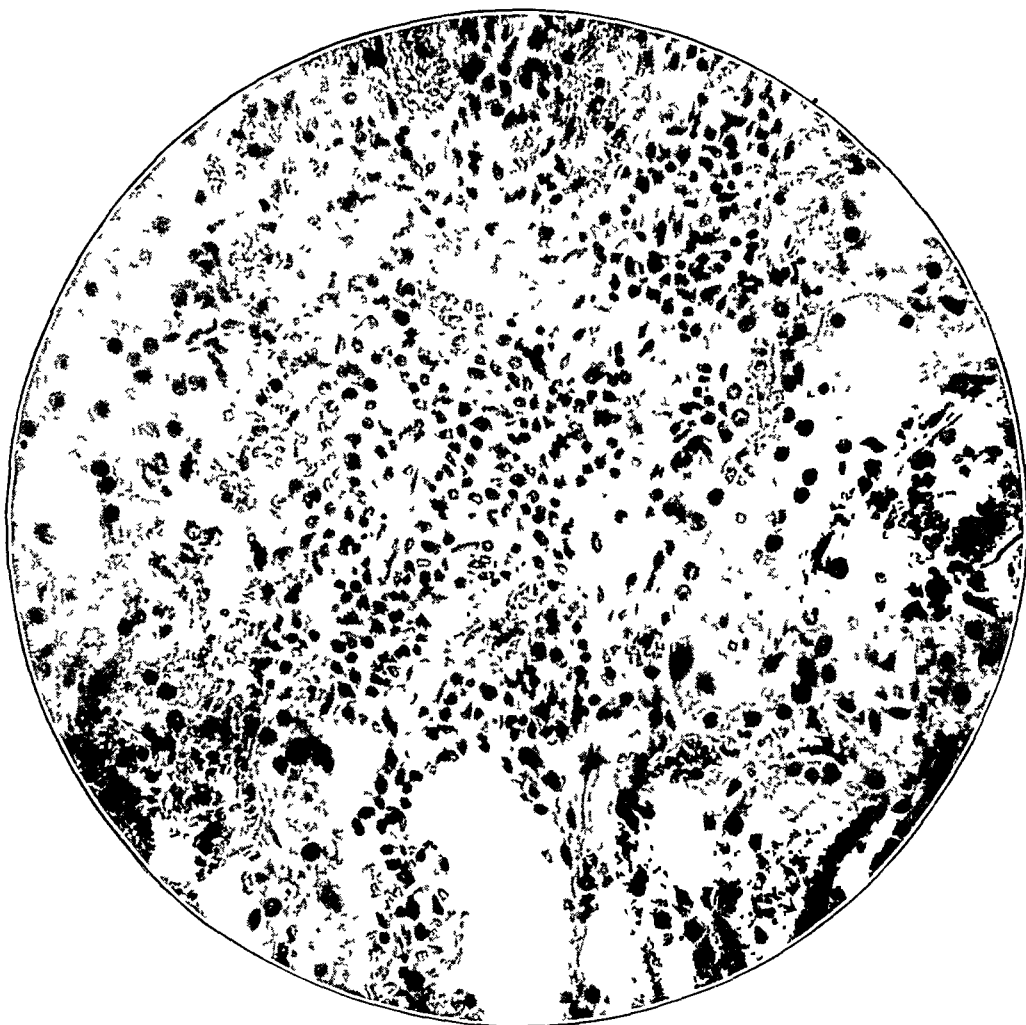
Fig. 4.—Kidney. Focal infiltration of lymphocytes and plasma cells between tubules.

Death from any cause is unusual in the early stages of rheumatic fever, but when it does occur rheumatic carditis with heart failure is the usual mechanism. In the present case, there was no clinical evidence of cardiac involvement. At the autopsy there was no gross pericarditis or endocarditis, and the heart was not enlarged. Microscopically the cellular infiltrations in the pericardium and endocardium

were small and scattered and not more impressive than those in other organs, such as the liver, where they could not reasonably be regarded as evidence of enough disease to affect seriously the function of the organ.

The problem arises of weighing the relative importance of the renal and the pulmonary lesions in causing death. The sustained urinary output and the receding azotemia indicate clearly that the patient did not die in a state of renal insufficiency. The slight generalized edema
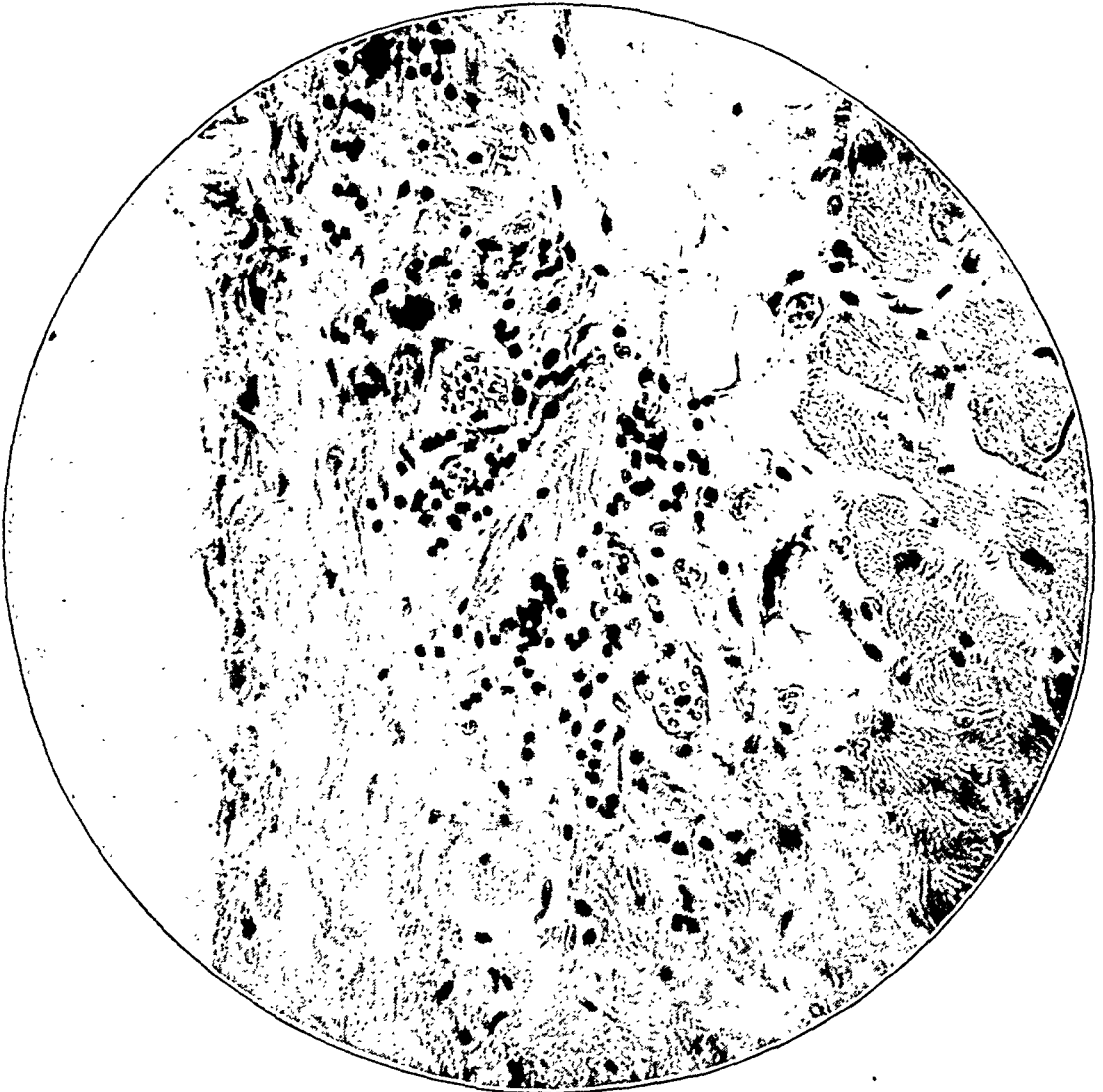
Fig. 5.—Heart. Small infiltrations of lymphocytes and plasma cells in pericardium. High power (× 380).

with lowered serum protein indicates edema chiefly from deficiency of albumin in the circulating blood. Some of this albumin was lost through the kidney. Much of it may well have been into the pulmonary space, as careful attention to the weight and the microscopic pathologic changes of the lungs will show. It seems impossible to assign the kidneys more than a secondary role in causing death. The clinical impression of death due primarily to pneumonitis was fully sustained by the

observations at autopsy. Such a case afforded an unusual opportunity to study the pulmonary lesions of rheumatic fever uncomplicated by secondary infection or by the changes secondary to heart disease.

NONSUPPURATIVE TISSUE LESIONS FOLLOWING STREPTOCOCCIC INFECTIONS

When pulmonary lesions occur in rheumatic fever, they are fundamentally like those occurring elsewhere in the body at the same time.
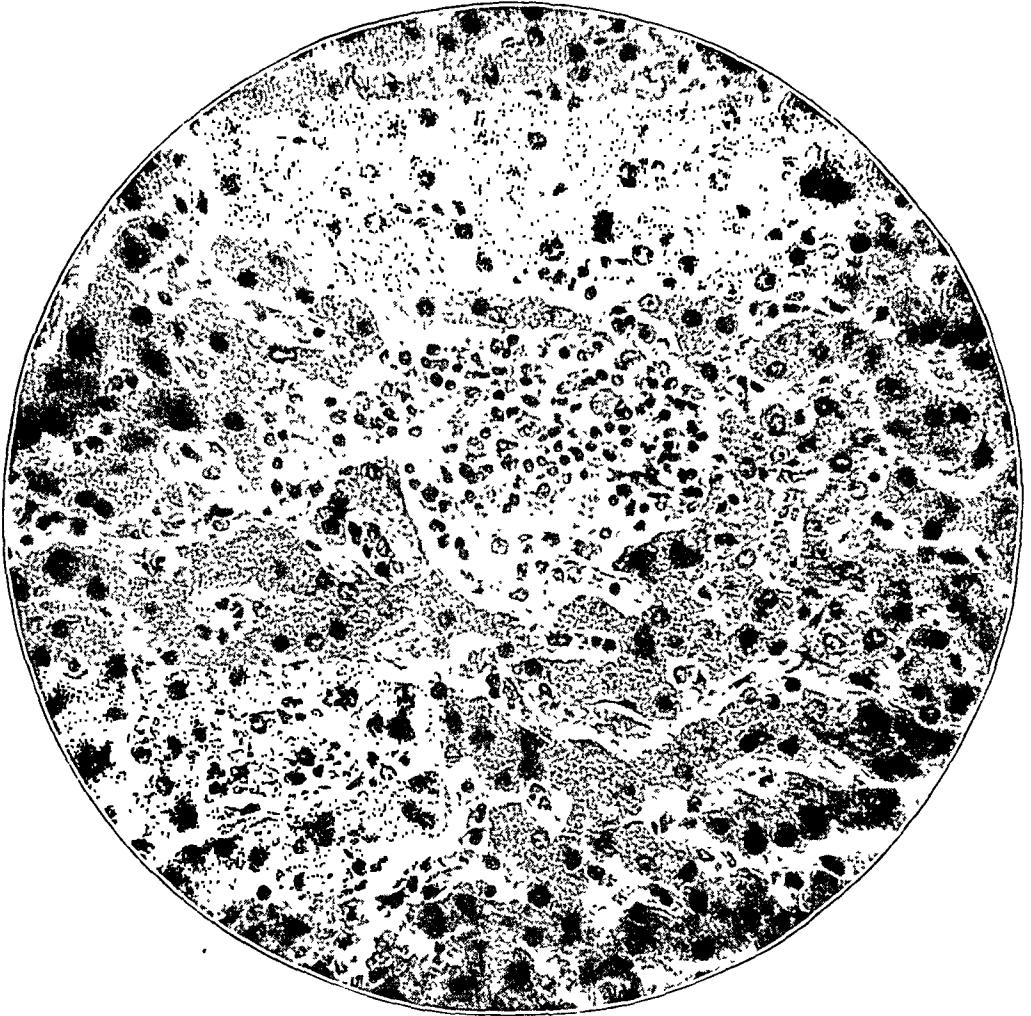
Fig. 6.—Liver. Small focal collection of lymphocytes and plasma cells, illustrative of the small lesions in many organs. High power (× 380).

The general similarity of the lesions in acute hemorrhagic nephritis, acute rheumatic carditis, chorea and many other conditions known to follow hemolytic streptococcus infections, has long been recognized. Some review of these general pathologic changes may be desirable to clarify the discussion of rheumatic pneumonitis which will follow

Of all persons who contract an infection with a hemolytic streptococcus, the great majority recover promptly and completely. Most such infections occur in the upper respiratory tract. The initial stage of acute invasion is a stage of suppuration, at least microscopically, and a small percentage of patients have additionally an immediate suppurative complication, such as lymphadenitis or otitis media. Particularly when the portal of entry is elsewhere than the upper respiratory tract, as in puerperal infection, a few may die after an acute, fulminating course, a septicemia. In such cases, streptococci are easily recoverable from the blood during life and demonstrable after death in the tissues, within capillaries or beyond the endothelial barrier, undergoing active phagocytosis by leukocytes or by cells of the reticuloendothelial system.

In a few who apparently recover or are recovering well from the acute invasive and suppurative stage there develop after a short clinical delay symptoms of nonsuppurative disease somewhere in the body. This latent period or delay varies from a few days to a few weeks. It is usually an afebrile period, but, particularly when the suppurative stage has been prolonged, it may not be perceptible clinically as a period of improvement. Depending on the organ or tissue most involved, this nonsuppurative stage may be expressed as acute arthritis, acute rheumatic carditis, acute hemorrhagic nephritis, acute encephalitis (chorea) or acute pneumonitis, frequently with manifestations less well defined or at least less well named as specific diseases, such as purpura, urticaria, erythema and generalized mild edema without much nephritis. Combinations are frequently present in a given subject.

Death in the latent period or in the early stages of the nonsuppurative sequels is so unusual that autopsies allowing study of the lesions are scarce. Study of them has been further hampered by the fact that the diseases concerned, such as acute rheumatic fever and acute hemorrhagic nephritis, were long regarded as unrelated processes. Realization has been slow in arriving that they are probably always relatable to an antecedent streptococcic infection, perhaps so mild as to escape attention as such.

Brody and Smith[1] and Mallory and Keefer[2] have reviewed the subject of these lesions and have added valuable contributions of their own from fatal cases of hemolytic streptococcus infections of various clinical types, scarlet fever, erysipelas, puerperal sepsis and cellulitis. Beginning a few days after the onset of the infection, there appear in many tissues foci of cellular infiltration composed chiefly of lymphocytes and plasma cells, with a few leukocytes often present and occasion-

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1. Brody, H., and Smith, L. W.: The Visceral Pathology in Scarlet Fever and Related Streptococcus Infections, Am. J. Path. **12**:373-394 (May) 1936.
2. Mallory, G. K., and Keefer, C. S.: Tissue Reactions in Fatal Cases of Streptococcus Haemolyticus Infection, Arch. Path. **32**:334-355 (Sept.) 1941.

ally a few eosinophils. The lesions are basically the same in all organs, regardless of whether the initial infection is in the form of scarlet fever or of another clinical type.

These lesions do not contain organisms and do not become abscesses. Preceding the actual infiltration of cells, there is localized damage of tissue. "Collagen necrosis" is a more specific term, preferred by the pathologist. If this is in a highly vascular organ or involves the wall of a small vessel, petechial hemorrhage is likely. Thus the petechial hemorrhage is the earliest lesion easily recognizable, although the peculiar focal collections of cell types previously described are more characteristic. Early and late lesions may be found in the same organ, indicating repetition in different places. The Aschoff nodule is a slightly later lesion, a special form of it occurring in the heart. It probably does not acquire its complete characteristics, detailed descriptions of which are so cherished by the histopathologist, until at least three weeks after the clinical onset of rheumatism.

The lesions are perhaps more plentiful in the heart and kidneys in most cases, although naturally these organs have received more attention because of the rather distinct clinical syndromes produced when either one or the other is predominantly involved, acute rheumatic carditis or acute hemorrhagic nephritis. Many of the lesions are in close relation to the vascular system, near small arteries, sometimes subintimal in veins and subendocardial in the heart. This relation to the vascular system is one reason that kinship is believed by some to exist between rheumatic fever and conditions such as periarteritis nodosa and generalized lupus erythematosus. The impossibility of resting the heart muscle or its valves completely may in part determine the usual frequency of lesions in it, and the great vascularity and unceasing activity of the kidneys may condition the frequency and prominence of lesions in these organs. But anatomy alone does not explain the observed variations in involvement of organs. Neither does there seem to be any connection between the organ involved and the particular strain of hemolytic streptococcus causing the initial infection, although this phase of the problem has not yet received exhaustive study.

Although connection between these nonsuppurative lesions and hemolytic streptococcus infection may be regarded as established, many phases of this relationship are still mysterious. Their general similarity to certain lesions occurring in anaphylactic states has long been noted. In recent years, Rich and Gregory [3] have stressed the factor of anaphylaxis in rheumatic fever and have secured admirable reproductions in rabbits

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3. Rich, A. R., and Gregory, J. E.: On the Anaphylactic Nature of Rheumatic Pneumonitis, Bull. Johns Hopkins Hosp. **73**:465-478 (Dec.) 1943; Further Experimental Cardiac Lesions of the Rheumatic Type Produced by Anaphylactic Hypersensitivity, ibid. **75**:115-134 (Aug.) 1944.

of the cardiac lesions by sensitization with foreign protein. Todd[4] and Coburn and Pauli[5] have studied the abnormal rise in serum antibodies coincident with the appearance of symptoms in rheumatic fever. Investigations in this field demonstrate that the lesions in this disease must be related in some way to abnormal antigen-antibody reactions, and thus rheumatic fever at last seems firmly bound to the hemolytic streptococcus. Opportunity may still remain to uncover some additional infectious agent, perhaps working in harmony with the streptococcus; but it is difficult to understand how the bond between rheumatic fever and the streptococcus can ever be entirely broken. No attempt will be made here to discuss at length this aspect of the problem because it is aside from the primary purpose of this paper.

PULMONARY LESIONS IN RHEUMATIC FEVER

It is probable that the pulmonary lesions are seldom extensive. It is possible that their importance is sometimes overlooked, particularly when they occur without other manifestations of rheumatic fever to call attention to their true nature. With this possibility as justification, detailed discussion of rheumatic lesions as they occur in the lung will now be given.

The lesions in the lung are not fundamentally different from those occurring elsewhere: focal damage of tissue, edema, possible capillary rupture, cellular infiltrations and efforts at healing. The immediate consequences of this in the lungs may be remarkably different from those in other organs, particularly if the lesions are severe. As naked exposure as possible of the capillaries to the air is the primary mission of the lung. Stroma is reduced to the necessary minimum around the alveolar capillary. This offers unusual opportunities for exudative phenomena. Partial damage to a capillary wall leads to the escape of small amounts of fluid higher in protein than simple edema fluid. With severer damage, there is capillary rupture and hemorrhage. In either case the release of fluid is easier than with a comparable degree of damage in a more solid organ. Further, such escaped fluid is dispersed easily in the porous lung, assisted by respiratory movements of lung and air, sometimes to points remote from the place of release. This accounts for the frequent finding of blood or the hyaline membrane in microscopic fields where there is no apparent capillary damage or

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4. Todd, E. W.: Antihaemolysin Titres in Haemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, Brit. J. Exper. Path. **13**:248-259 (June) 1932.

5. Coburn, A. F., and Pauli, R. H.: Studies on Relationship of Streptococcus Hemolyticus to Rheumatic Process: Observations on Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, J. Exper. Med. **56**:651-676 (Nov.) 1932.

cellular infiltration, for the hyaline membrane is merely partially inspissated fluid of higher protein content than usual edema fluid, impacted against the lining of the air ducts by forcible inspirations. The kidney is also a highly vascular organ, and in one way the manifestations of this disease in it are roughly comparable to the situation in the lung. Many renal capillaries are so close to an open tubular system that capillary seepage, whether as albuminous fluid or as whole blood, is unimpeded once the tubular wall is penetrated or broken. For purposes of exposition only, the hyaline membrane of the lung may be likened to the hyaline cast of the kidney tubule. Coburn[6] has shown that with routine Addis counts of the urinary sediment one may detect abnormal hematuria in most cases of rheumatic fever, indicating that in most cases there is renal involvement. A comparably sensitive test of the lungs might give surprising results. Exudative changes would have to be considerable to show roentgenographically.

SIMILARITY BETWEEN PATHOLOGIC CHANGES OF RHEUMATIC PNEUMONITIS AND OF VIRUS PNEUMONITIS

While pneumonitis is being more frequently recognized in cases of severe rheumatic fever, it is not often described as dominating the clinical picture. Since rheumatic carditis is sometimes recognized as occurring without arthritis and since acute nephritis frequently occurs in the postinvasive stage of streptococcic infection, with or without arthritis, there is no good reason why pneumonitis should not occur sometimes as the only prominent clinical exhibition.

It is my belief that this occurs more often than is suspected and that the condition is mistaken for virus infection of the lungs. An illustrative case is that of a young man known to have had a normal heart at the time of his enlistment in the Navy and later at the time of his admission to a Naval hospital with a diagnosis of primary atypical pneumonia. No rheumatic pains were noted at the time. He was discharged as well and fit for duty after twenty-six days, after a clinical course that might be described as average for this condition. Nine months later he was readmitted to the hospital with well advanced mitral and aortic valvular lesions. Review of the older record then indicated that the only reasonable explanation of the former pneumonitis was that it was the only prominent clinical manifestation of "rheumatic" fever which he had at the time. When one examines the literature on primary atypical pneumonia, with particular attention to protocols of cases, suggestive evidence is sometimes encountered that some of the cases included under this term may well have been cases of rheumatic pneu-

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6. Coburn, A. F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, Am. J. Dis. Child. **45**:933-972 (May) 1933.

monitis unrecognized as such. Thus one author,[7] reviewing 32 cases, described 1 in which a cold in the head preceded the onset of pneumonitis by ten days and the heart was without murmurs at the onset of the illness, but after a protracted convalescence of two months a presystolic murmur and cardiac enlargement led to the conclusion that the patient had had rheumatic heart disease. In another report[8] the authors, reviewing 52 cases of what would now be called primary atypical pneumonia, mentioned a group of 6 cases in which the primary disease was "complicated by a variety of phenomena suggesting that tissues other than the pulmonary alone were involved. Among these phenomena were migratory polyarthritis, erythematous skin eruptions, slight enlargement of the spleen and lymph glands, jaundice, gross hematuria, fibrinous pericarditis and encephalitis." In a fatal case from this series, periarterial lesions suggesting periarteritis nodosa were found. Examples such as these are cited merely as evidence for a suspicion that conditions of diverse origins have been unwittingly grouped together under the poor term "primary atypical pneumonia," and that at least a small proportion of such cases have been cases of rheumatic pneumonitis without much rheumatism. I freely admit a suspicion of my own guilt in this respect, and I wish that I now had available for reevaluation records of several cases in my own experience in recent years.

That the clinical resemblance between rheumatic pneumonitis in some cases and pneumonia due to virus infection may depend more than is realized on a rather striking resemblance of pathologic anatomy may be emphasized by a brief chronologic review of the development of our knowledge of them.

Pathologic Changes of Influenzal Pneumonia.—The pathologic changes of influenzal pneumonia in 1918-1919 were described by many authors and particularly well by MacCallum,[9] Goodpasture and Burnett[10] and Wolbach.[11] The essential lesion was that of damage to tissue with rupture of capillaries, formation of hyaline membrane and infiltrations of mononuclear cells. In severely ill patients dying quickly, hemorrhage was the prominent feature. In those surviving longer, secondary infection with pyogenic organisms was the rule, and there

7. Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X), Bull. Johns Hopkins Hosp. **67**:268-305 (Oct.) 1940.

8. Kneeland, Y., Jr., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, Bull. Johns Hopkins Hosp. **67**:229-267 (Oct.) 1940.

9. MacCallum, W. G.: Pathology of Pneumonia Following Influenza, J. A. M. A. **72**:720-723 (March 8) 1919.

10. Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13**:177-197, 1919.

11. Wolbach, S. B.: The Pathology and Bacteriology of Fatal Influenza Cases at Camp Devens, Bull. Johns Hopkins Hosp. **30**:104-109 (April) 1919.

was corresponding. leukocytic or suppurative exudation. Either excessive hemorrhage or much suppuration tended to blur the underlying picture. For a long time this picture, particularly when the hyaline membrane was present; was regarded as almost pathognomonic of influenzal pneumonia.[12] Farber and Wilson [13] in 1932 demonstrated the true mechanism of production of this membrane and so its lack of specificity. It is now realized that while this membrane is not usually observed by histologic examination in routine autopsies and should arrest attention when encountered, it is not pathognomonic of any one disease.

Rheumatic Pneumonitis.—The characteristic pathologic changes in rheumatic pneumonitis were first described with reasonable clarity by Naish,[14] in 1928, and by Gouley and Eiman,[15] in 1932. More recently, Epstein and Greenspan [16] have further elaborated the description of these changes and. have traced the evolution of the lesions beyond the acute phase. In all descriptions there is much similarity to the basic lesions in influenzal pneumonia.

Primary Atypical Pneumonia.—Under this awkward term there have been described in recent years many cases of pneumonia not caused by an identified organism and often thought due to a virus, although there is no agreement that a specific virus has been isolated. There are several reports of the pathologic anatomy of this based on 1 or a few cases, but that of Golden,[17] based on 42 acceptable cases from the United States Army, is the most comprehensive. The lesions may be complex, depending on the duration and probably on the presence or absence of secondary infection. Generally the descriptions resemble those given of influenzal pneumonia in 1919, although there are few instances of the acute, fulminating form of the disease in which the patient dies quickly with wet, bloody lungs, so common in the epidemic of that time. Probably because in few of the fatal cases have the patients died quickly, suppurative bronchiolitis with bronchopneumonia is a prominent observation, but the focal tissue lesions with infiltrations of mononuclear cells are also present.

12. Goodpasture, E. W.: The Significance of Certain Pulmonary Lesions in Relation to the Etiology of Influenza, Am. J. M. Sc. **158**:863-870 (Dec.) 1919.

13. Farber, S., and Wilson, J. L.: The Hyaline Membrane in the Lungs: II. An Experimntal Study, Arch. Path. **14**:450-460 (Oct.) 1932.

14. Naish, A. E.: The Rheumatic Lung, Lancet **2**:10-14 (July 7) 1928.

15. Gouley, B. A., and Eiman, J.: The Pathology of Rheumatic Pneumonia, Am. J. M. Sc. **183**:359-381 (March) 1932.

16. Epstein, E. Z., and Greenspan, E. B.: Rheumatic Pneumonia, Arch. Int. Med. **68**:1074-1094 (Dec.) 1941.

17. Golden, A.: Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined": Acute Interstitial Pneumonitis, Arch. Path. **38**:187-202 (Oct.) 1944.

Other Virus Pneumonias.—The pathologic changes in certain rare types of virus pneumonia, so far as they have been well described, are in general like those in influenzal pneumonia. In psittacosis distinctive inclusion bodies are found, and in certain rare types of pneumonia in infants inclusion bodies have been described by experienced observers,[18] but in influenzal pneumonia and in the disease now called primary atypical pneumonia true inclusion bodies are not present. Thus most types of virus infections in the lung leave no individual signatures observable by histologic examination.

General Comment on Pathologic Changes.—Much time has here been devoted to pathologic anatomy because one must understand this well in order to understand any disease and because often-one must use it as a point of departure, at least, in arranging any scheme for differential diagnosis. The manner of this presentation has been purposely arranged to emphasize similarities, to warn of the pitfalls that may await if one attempts to depend too much on physical findings or roentgenographic appearance or even the general clinical course in cases of mild infections in which similarities are particularly striking.

The emphasis here given to the resemblance between rheumatic and virus pneumonitis may seem to revive the question of virus origin of rheumatic fever. It is not so intended. Some may still be dissatisfied with the streptococcus as the sole culprit in rheumatic fever, and recent observations[19] have suggested the possibility of a virus agent. Discussion of this is purposely avoided here because the final answer is not obtainable from anatomic changes alone, which this presentation stresses. Admittedly not all aspects of the disease which is today called rheumatic fever are clear. The subject of primary atypical pneumonia also is confusing. But enough is known so that better attempts might be made to sort cases, if only in terms of current terminology.

CLINICAL DIFFERENTIATION BETWEEN RHEUMATIC PNEUMONITIS
AND PRIMARY ATYPICAL PNEUMONIA

Since the anatomic pictures of primary atypical pneumonia and of that occurring as a nonsuppurative sequel to hemolytic streptococcus infection are so alike, it is little wonder that clinical distinction between them may be difficult if there is no clue outside the lungs. In each

18. Goodpasture, E. W.; Auerbach, S. H.; Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. **57**:997-1011 (May) 1939.

19. Eagles, G. H.; Evans, P. R.; Fisher, A. G. T., and Keith, J. D.: A Virus in the Aetiology of Rheumatic Diseases, Lancet **2**:421-429 (Aug. 21) 1937. Eagles, G. H., and Bradley, W. H.: Agglutination of Suspensions of Virus-Like Particles Prepared from Exudates in Acute Rheumatic Fever, Quart. J. Med. **8**:173-184 (April) 1939. MacNeal, W. J.; Blevins, A.; Slavkin, A. E., and Scanlon, H.: Experimental Verrucous Endocarditis, Science **101**:415-416 (April 20) 1945.

there is fever and cough, with hemoptysis if the condition is severe. Physical and roentgenologic signs are similar, with a tendency to patchy distribution and to recurrence or migration. Examination of the sputum would be of little help, for, while a certain proportion of the patients with rheumatic pneumonitis retain some hemolytic streptococci in the sputum, many healthy persons as carriers also have them. The blood sedimentation rate is high in each.

Clinical Differences Between Rheumatic Pneumonia and Primary Atypical Pneumonia.—Perhaps the best general plan of distinguishing in an individual case would be the deliberate effort to secure additional clinical evidence of nonsuppurative lesions elsewhere in the body, to suggest that the case is one of rheumatic fever or of some other clinical sequel to streptococcic infection. Such evidence would include mild arthritic manifestations, hematuria, epistaxis, purpura, erythema marginatum, encephalitis and electrocardiographic changes or physical signs to indicate cardiac involvement. Since recurrence is common in rheumatic fever, the history of a previous attack might have weight in the making of a decision. The occurrence of a sore throat a few days or weeks preceding the onset of pulmonary symptoms might suggest the likelihood of a rheumatic type of involvement in the lungs, but direct inquiry may be needed to obtain such a part of the history.

Laboratory Tests.—Two procedures of possible merit are worth suggesting. In many cases of primary atypical pneumonia there is a high titer of cold agglutinins in the serum.[20] This is not described in rheumatic fever. In most cases of acute rheumatic fever there is a rise in antifibrinolysin and antistreptolysin in the blood.[21] Procedures to determine the presence of these substances might prove useful in this particular diagnostic problem.

<div align="center">SUMMARY</div>

A case of rheumatic fever is presented in which death, due primarily to the pulmonary lesions of this disease, occurred thirty days after the onset of acute pharyngitis and fifteen days after the onset of rheumatic pain. Pathologic changes in the lungs and kidneys are described in detail.

The tissue lesion in rheumatic pneumonitis is interpreted as the same as that sometimes occurring in many organs as a nonsuppurative

20. Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinis (Auto-hemagglutinins) in Primary Atypical Pneumonias, Science **97:**167 (Feb. 12) 1943. Humphrey, A. A.: Cold Hemagglutination Test in Diagnosis of Primary Atypical Pneumonia, U. S. Nav. M. Bull. **43:**1117-1127 (Dec.) 1944.

21. Boisvert, P. L.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19:**65-74 (Jan.) 1940. Bunim, J. J., and McEwen, C.: The Antistreptolysin Titer in Rheumatic Fever, Arthritis and Other Disease, ibid. **19:** 75-82 (Jan.) 1940.

sequel to infection with a hemolytic streptococcus, whether or not the disease is expressed clinically with rheumatism. Clinical syndromes caused by such lesions, depending on the organ predominantly involved, may be called acute hemorrhagic nephritis, acute rheumatic fever, acute encephalitis (chorea) or one or another of several other clinical conditions not usually named as if specific diseases.

The similarity between the pathologic anatomy of rheumatic pneumonitis and of so-called primary atypical pneumonia is pointed out, and reasons are given for suspecting that in some cases rheumatic pneumonitis is being mistakenly called primary atypical pneumonia. Means for differentiating them clinically are briefly indicated.

DANGER OF INTRAVENOUS INJECTION OF PROTEIN SOLUTIONS AFTER SUDDEN LOSS OF RENAL TISSUE

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I N cases of shock there may be a sudden loss of effective renal tissue, because for a time the kidney does not get enough blood; more sustained deprivation sometimes occurs after transfusion reactions; there are instances of anatomic as well as functional loss, as when part of the kidney is destroyed by shell fragments, and in glomerular nephritis and symmetric necrosis of the cortex the majority of the nephrons in a short space of time may become functionless and many may be irrevocably destroyed. For each of these situations there is a specific treatment dependent on knowledge of the causative mechanism, but in all, except the most transitory instances of functional loss, we believe that the work demanded from the remaining renal tissue should be reduced. The work of the kidney consists almost wholly in the reabsorption of water from a concentrated solution of urea in the tubules into a relatively dilute solution of urea in the blood. Rest is achieved when a diet that induces a low rate of urea excretion is given and when enough water is taken to keep the urine dilute. Rest is needed when accident or disease suddenly reduces the size of the kidney, because the enzyme systems that transfer water against osmotic pressure are limited in quantity and capacity. The remaining still functioning remnant of kidney then works at top speed, but if rest is not given one finds the signs of "renal failure" appearing in the form of a rapidly rising concentration of nitrogenous metabolites in the blood, and when the overload of work continues there follow proteinuria, cylindruria, anemia, hypertension and finally death in uremia.[1]

A sudden loss of renal tissue, the essential feature of the general situation which we are discussing, can be experimentally reproduced by removing three quarters of the total kidney.

1. Addis, T.: The Osmotic Work of the Kidney and the Treatment of Glomerular Nephritis, Tr. A. Am. Physicians 55:223, 1940.

We chose thirty day old rats as subjects because they are more sensitive than older rats to a sudden reduction in the number of nephrons.[2] Eighty-six males were selected from the colony. They had been living on a diet which contained 17 per cent of protein. After one kidney and half the remaining kidney had been excised, the rats were divided into four groups. The first group was given no protein, the second 22.6 per cent and the third 64.1 per cent of protein in the form of lactalbumin. The substrate of all the diets was a starch-lard mixture enriched with ample quantities of vitamins and minerals. Since the variation in protein concentration was obtained by replacing starch with lactalbumin, all these diets were approximately isocaloric. Water was given ad libitum.

The mortality rates during the seven days after operation are given in table 1. These rats died forty-eight hours or more after the operation. We proved that uremia was the cause of death by measuring the urea concentration in the tissues of those which had only recently died.

TABLE 1.—*Death Rate from Uremia, Determined by the Demand for Work Imposed by an Increasing Protein Consumption After Removal of Three Fourths of Kidneys*

Protein, Gm. per Day	Number of Rats	Died in Uremia	Per Cent Mortality
0.00	10	0	0
1.67	15	2	13
2.38	49	21	43

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2. After a large loss of renal tissue young rats are more likely than old rats to die of uremia. We think that this is because the younger the rat the greater is the food protein consumption per unit of body size (MacKay, E. M., and MacKay, L. L.: Age and the Effect of Unusual Diets, J. Biol. Chem. **86**:765 [April] 1930). Young rats certainly do not die because their restoration of lost renal tissue is slower (MacKay, L. L.; MacKay, E. M., and Addis, T.: The Effect of Various Factors on the Degree of Compensatory Hypertrophy After Unilateral Nephrectomy, J. Clin. Investigation **1**:576 [Aug.] 1925) or because their vascular system is less able to adapt itself to sudden change. In both these respects 30 day old rats are more capable than 300 day old rats. There is thus an interesting divergence in the effect of age when one compares mortality rates in the uremia following a high protein consumption after partial nephrectomy and the uremia that follows ligation of the vena cava (Addis, T., and Raulston, B. O.: A Reversible Form of Experimental Uremia, Tr. A. Am. Physicians **45**:318, 1930). In older rats death due to uremia, after 75 per cent of the kidney has been removed, is not common under any conditions. The reverse is true when the vena cava is tied above the entrance into the renal veins. Ninety per cent of the old rats die of uremia, while all the young ones survive (Addis, T., and Lew, W.: Age and the Rate of Venous Enlargement Under Increased Venous Pressure, Proc. Soc. Exper. Biol. & Med. **42**:602 [Nov.] 1939). In this case life or death depends primarily on the rate at which there is an enlargement of venous channels through which blood from the kidney can pass from the closed vena cava into veins that run up the abdominal wall and reach the heart above the occlusion. This is a situation that tests the adaptability of the venous system, and in this capacity young rats are clearly superior.

In every case we found more than 500 mg. of urea per hundred grams of tissue. The rate of death in uremia varied with the amount of protein consumed: no deaths after no protein, 13 per cent after 1.67 Gm. and 43 per cent after 2.38 Gm. of protein a day. The protein taken was lactalbumin, but the mortality was not a consequence of any deleterious effect of this particular protein. That is shown by another exactly similar experiment on 30 day old rats which were given 86 per cent casein instead of 86 per cent lactalbumin. The mortality rate was 47 per cent.

On the sixth day after the operation the survivors were placed in special cages, in which they were given free access to their respective diets while the urine was collected on blotting paper. At the end of the twenty-four hour period and seven days after the operation, urine was collected directly from the bladder for determinations of the urea concentration in the urine. The rats were then anesthetized with ether; blood was collected, and measurements of weights of organs were made.[3]

TABLE 2.—*Effect of Increasing Demand for Work Through Increasing Protein Consumption on Kidneys Reduced to Quarter of Original Size Seven Days Before Measurements Were Made*

Group	Protein, Gm. per Day	Changes of Body Weight, per Cent of Original Weight	Kidney Protein Corrected for Body Weight, Mg.*	Urea Excretion, Mg. per 24 Hr.	Serum Urea Concentration, Mg. per 100 Cc.	Urea Clearance, Cc. per 24 Hr.	Urea Work, Calories per 24 Hr.
First........	0.00	—22	34	42	57	74	0.8
Second......	1.67	+ 5	37	102	65	157	2.5
Third.......	2.38	—33	42	402	274	147	6.0

* The weights of kidney protein were corrected for the differences in body weight by deriving the amounts to be expected in a 50 Gm. rat by multiplying the observed amounts by $\dfrac{50^{0.7}}{BW^{0.7}}$.[3] This particular method of correction contributes to the precision of the results, but qualitatively similar conclusions are obtained even when such simple but inaccurate expressions as the number of milligrams of kidney protein per hundred grams of body weight are used.

The results are given in table 2. On comparing the three groups in table 2, it was at once apparent that the rats in the third group, which had eaten the most protein, were all sick. In a week they had lost 33 per cent of their original body weight, although, when we measured their food consumption on the last day, they were taking an adequate number of calories. Their miserable state arose because they were dying of uremia. The 274 mg. of urea per hundred cubic centimeters that we found in their serum was only part of a more general store of retained metabolites. Thus, the creatinine concentration had risen to 4.02 mg. per hundred cubic centimeters, an extremely high level for rats. After the ingestion of 86 per cent of casein, due

3. Walter, F., and Addis, T.: Organ Work and Organ Weight, J. Exper. Med. **69**:467 (March) 1939.

to which the death rate was 47 per cent, the serum urea concentration of the survivors was 320 mg. per hundred cubic centimeters. It is evident that under these conditions the consumption of even the usual amount of protein may induce renal failure.

At first glance it may seem curious that we describe the situation found in the third group as one of "renal failure" when table 2 shows that the kidneys of the animals in this group succeeded in excreting almost ten times as much urea as those of the first group; it may seem perverse to ascribe this failure to an incapacity to do osmotic work when they actually did seven and a half times as much work as the kidneys which we say were successful, and paradoxic to designate as "insufficient" those that cleared twice as much urea as those of the first group. These failing kidneys constructed more new renal tissue than those of the other groups; hence, in the end they were larger and more capable than the others and were equally devoid of any sign of structural defect. But this difficulty arises only because of the natural but erroneous tendency to regard the kidney as a more or less autonomous organ. One is inclined to think of it abstractly in separation from the body, as though it were an organ like the eyes or ears, which, though proportioned to the rest of the body, are, in the main, fixed and given through inheritance. In the kidney, however, there is no approach to such autonomy. Absolute significance cannot be attached to isolated measurements of the structure or function of the kidney. Their meaning lies in their relation to the amount of work that has been imposed. Thus, if one asks what size of kidney is proper for a rat with a body weight of 150 Gm. one finds kidneys whose average weights vary from each other by as much as 66 per cent. It is only through the constant ingestion of a diet that induces some uniformity in osmotic work that there is an approach to the usual degree of constancy that exists between a part and the whole of the body. If the blood urea concentration is taken as a measure of function and we are asked what variation in the level of concentration was to be expected in rats with entirely normal kidneys, we should have to say that we had observed concentrations that varied all the way from 5 to 500 mg. per hundred cubic centimeters. Consequently, the figures in table 2 have to be interpreted in the light of the demand for work from the kidney that was left. Since the number of nephrons had been reduced to a quarter of their original number, the remaining nephrons in each group were called on to do four times as much work as before. Then we went on to vary the demand for work by changing the consumption of protein, and we found that as the demand increased there was an increase in the rate of urea excretion and an acceleration in the rate of formation of new renal tissue and that the amount of work actually done was increased. But the remaining

fragments from which most work was demanded did not grow fast enough, and the work done was inadequate to the demand; hence, uremia supervened, and many died. It was a real failure, but it was relative, not absolute.

From these experiments we must conclude that in young rats suddenly deprived of most of their kidneys even a moderate consumption of protein may induce renal failure and death. Since we know of no evidence that the kidney of a man is fundamentally different from that of a rat because a man's kidney works in the same way and fails in the same way, the amount of protein given to men who have suffered a sudden and serious loss of renal tissue becomes a matter of real concern. If one considers first the situation in which the loss is traumatic and accompanied with shock, the first therapeutic requirement is the reconstitution of a normal circulation. The nature of any protein that may be injected for this purpose is important, because

TABLE 3.—*Urea Excretion (in Milligrams per Twenty-Four Hours) After 0.85 Per Cent NaCl and Injections of Protein*

			Injections		
Day	NaCl Solution	Gelatin	Horse Serum	Bovine Albumin	Rat Serum
First..............	114	190	173	118	163
Second............	63	154	100	70	47
Third.............	69	180	126	94	76
Fourth............	63	147	88	78	40
Fifth.............	57	142	110	85	67
Sixth.............	57	139	81	75	45
Seventh..........	48	179	126	84	64
Totals........	471	1,131	804	604	502

some proteins induce a considerable increase in urea excretion and thus increase the work required from the remaining fragment of kidney. In table 3 is given the average daily rate of urea excretion of a group of 15 rats with a body weight of 150 Gm. which at the beginning of the first, third, fifth and seventh days of the period of observation received an intraperitoneal injection of 5 cc. of 0.85 per cent sodium chloride solution per hundred square centimeters of body surface, a quantity corresponding to 900 cc. given to a man of 70 Kg. when estimated on the basis of body surface. This group received adequate calories but no protein because they were kept on 35 per cent dextrose in 0.4 per cent sodium chloride solution with added ·B vitamins. This is the control for other groups of 15 rats with a body weight of 150 Gm. kept on the same dextrose solution but given the same volume of 6 per cent protein solutions in the form of gelatin, horse serum, bovine albumin and rat serum.

Table 3 shows that the injection of certain proteins leads to greater increase in urea excretion than injection of others and that rat serum gives

the least increase. But it should be noted that on the days of injection even rat serum induces a 30 per cent increase over the control group. This raises the question as to how much increased urea excretion may follow the injection of human plasma into men. In our experiments on rats the protein starvation favored the utilization of the injected protein for the satisfaction of anabolic needs, and a large part was, in fact, so used. We have shown that rats can increase the total quantity of protein in their organs and tissues when intraperitoneally injected horse serum is their only source of material for the building of new protein.[4] But plasma and albumin often have to be given to men under conditions that are much less favorable for protein synthesis. All blood proteins are inadequate, and under the best conditions some loss of urea must be anticipated. When one injects 1 liter of whole blood, one gives approximately 167 Gm. of protein. If it contains 400 Gm. of red blood cells, which contain 30 per cent of protein, one gives 120 Gm., and if there is 670 Gm. of plasma one adds 47 Gm., a total of 167 Gm. When patients who have suffered a serious loss of renal tissue are given multiple injections of whole blood and plasma, as not infrequently happens, there may be danger of reproducing the conditions exemplified in table 1. To restore the circulation without imposing work on the kidney there is need in certain clinical situations for a purely carbohydrate substitute for blood plasma that is efficient and safe.

SUMMARY

1. After removal of three quarters of the total renal tissue from young rats there were no deaths when no protein was taken, but as the amounts of protein consumed increased there was an increasing number of deaths in uremia.

2. In the survivors there were no signs of renal failure when no protein was taken, but as the consumption of protein increased the concentrations of urea and creatinine in the serum rose toward uremic levels, although at the same time the rates of urea excretion, of urea clearance, of work accomplished and of new renal tissue constructed were all augmented. This was, therefore, not an absolute renal failure but one that was a failure only in relation to the demand imposed.

3. An increased demand for work from the kidney is imposed by the parenteral injection of any protein to a degree that varies with its nature and with the conditions under which it is administered.

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4. Addis, T.; Lee, D. D.; Lew, W., and Poo, L. J.: The Utilization of Parenterally Administered Horse Serum by the Rat, Am. J. Physiol. **128:** 544 (Feb.) 1940.

SULFADIAZINE AND PENICILLIN FOR HEMOLYTIC STREPTO-COCCUS INFECTIONS OF THE UPPER RESPIRATORY TRACT

An Evaluation in Tonsillitis, Nasopharyngitis and Scarlet Fever

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ACUTE infections of the upper respiratory tract due to hemolytic streptococci, while constituting an important health problem in a civilian population, become accentuated during the time of war. This applies particularly to groups of military personnel during the early training period. Several reports have recorded attempts to control hemolytic streptococcus infections in military personnel, and the efforts have not been without some success.[1] The use of the sulfonamide compounds in the treatment of streptococcic infections of the upper respiratory tract has resulted in conflicting reports concerning the effectiveness of these drugs.[2] Until the present investigation was

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1. Holbrook, W. P.: The Army Air Forces Rheumatic Fever Control Program, J. A. M. A. **126**:84 (Sept. 9) 1944. Coburn, A. F.: The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the U. S. Navy, ibid. **126**:88 (Sept. 9) 1944. Robertson, O. H.; Hamburger, M., Jr; Loosli, C. G.; Puck, T. T.; Lemon, M. M., and Wise, H.: A Study of the Nature and Control of Air-Borne Infection in Army Camps, ibid. **126**:993 (Dec. 16) 1944.

2. Rhoads, P. S., and Afremow, M. L.: Sulfanilamide in the Treatment of Sore Throat Due to Hemolytic Streptococci, with Controls, J. A. M. A. **114**:942 (March 16) 1940. Freis, E. D.: The Treatment of Tonsillitis with Small Doses of Sulfonamides, ibid. **126**:93 (Sept. 9) 1944.

initiated and completed, no well controlled studies of penicillin in the therapy of infections, of the upper respiratory tract, including scarlet fever, had appeared.   Plummer and colleagues[3] have recorded the results of penicillin therapy in 28 cases of acute pharyngitis-tonsillitis due to group A hemolytic streptococci. No patients with scarlet fever were treated.   There were 6 control patients who did not receive any specific therapy.   The authors called attention to the prompt improvement in patients following the intermittent, intramuscular injections of penicillin. But clinical relapses occurred in subjects treated for less than four days, and these relapses coincided with the reappearance of hemolytic streptococci in the nasopharynx.   In none of the treated patients did acute rheumatic fever develop.

The purpose of this report is to detail an evaluation of sulfadiazine and, especially, penicillin in the treatment of hemolytic streptococcus infections, such as nasopharyngitis, tonsillitis and scarlet fever.   In the initiation of this investigation, three primary objectives were kept in mind: first, to determine whether either sulfadiazine or penicillin shortened the clinical course of a given infection; second, to ascertain whether the number of complications of the disease, including acute rheumatic fever, was reduced by this specific therapy, and, third, to decide whether the treatment was associated with a prompt eradication of hemolytic streptococci from the nasopharynx.

METHODS OF STUDY

Clinical Material.—A total of 210 young men were observed in one training area between December 1943 and May 1944.   This included a control group of 102 patients, who did not receive either sulfadiazine or penicillin, 95 patients who were given penicillin or penicillin and sulfadiazine and 19 patients to whom only sulfadiazine was administered.   The types of hemolytic streptococcus infections which the patients in the three groups had will be described shortly.   All the men were considered ill enough by physicians at the dispensary to require hospital care.   The majority of patients were seen in the hospital shortly after the onset of their illness.   The patients were assigned to special wards for infections of the upper respiratory tract, where they were first examined by the officer on duty. Within twenty-four hours after entry each patient was seen by at least two members of the Commission on Hemolytic Streptococcal Infections.   The Commission obtained a history of the illness from each patient and recorded the results of a physical examination on a special form.   After bacteriologic studies or outstanding clinical features had determined that a person had an infection of the upper respiratory tract due to hemolytic streptococci, he was transferred to a ward specifically designated for patients with this type of infection.   Each of the patients with streptococcic infections was seen and examined by at least two members of the Commission once or twice daily, and clinical notes were made during the patient's stay in the hospital.

3. Plummer, N.; Duerschner, D. R.; Warren, H. D.; Rogliano, F. T., and Sloan, R. A.: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, J. A. M. A. **127**:369 (Feb. 17) 1945.

Usually the patients did not receive specific therapy until precise bacteriologic data were available. In preliminary treatment the administration of any antipyretics was avoided, and the discomfort of the patients was relieved with barbiturates, codeine sulfate and irrigation of the throat with hot saline solution.

All the patients were arbitrarily divided into three clinical groups. A patient was considered to have tonsillitis when there was definite objective evidence of redness, edema, swelling and exudate involving the tonsillar tissue. Patients with nasopharyngitis constituted a group with and without tonsils but in whom the tonsils did not appear to be primarily involved. Patients with scarlet fever included those who had either tonsillitis or nasopharyngitis but in whom a characteristic dermal rash was present.

Bacteriologic Studies.—Material from the nasopharynx and oropharynx was obtained by swabbing the cavities with cotton-tipped applicators and were then cultured by inoculation of mule blood agar plates. The plates were streaked with a platinum wire loop and incubated aerobically at 37 C. for eighteen to twenty-four hours. The degree of growth of hemolytic streptococci on the plates was quantitated from a minimum growth of 1 plus to a maximum growth of 4 plus. Representative hemolytic colonies were picked and grown on mule blood agar plates and then grown in pure culture in liquid culture mediums. Identification of the group to which the individual strains belonged was determined by the method of Lancefield,[4] while the typing of group A strains was performed according to Lancefield's technic.[5] Materials for cultures were obtained periodically, sometimes daily, from each of the patients during his hospitalization. Grouping and typing of hemolytic streptococci isolated in all cultures were carried out. Arrangements were also made for the majority of the patients to return for a clinical and bacteriologic check-up two to three weeks after discharge from the hospital. Approximately 2,000 cultures of material from the nose and throat were studied during the course of this investigation.

Miscellaneous Laboratory Studies.—In addition to the foregoing bacteriologic investigations, technical assistants in the laboratory of the Commission made total and differential leukocyte counts of the blood before, during and after specific therapy. Serial electrocardiograms were obtained on many of the patients during their period of hospitalization and in some instances after discharge from the hospital. Sedimentation rates of the erythrocytes were determined at intervals on the majority of the patients according to the method of Westergren.[6] Dick tests were applied on a patient's admission to the hospital and then during the stage of convalescence. An analysis of the Dick reaction in these patients constitutes part of a subsequent report. This also applies to the results of several different serologic tests.

Sulfonamide Therapy.—A group of the more seriously ill patients were treated with standardized doses of sulfadiazine by the oral route. An initial dose of 3 Gm. of sulfadiazine was given and then 1 Gm. every four hours until the temperature approached normal. Then 1 Gm. was given every six hours for twenty-four hours. As a prophylactic measure against renal complications from sulfadiazine, the daily

4. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571 (April) 1933.

5. Swift, H. F.; Wilson, A. T., and Lancefield, R. C.: Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. **78**:127 (Aug.) 1943.

6. Westergren, A.: The Technique of the Red Cell Sedimentation Reaction, Am. Rev. Tuberc. **14**:94 (July) 1926.

fluid intake and output were charted for each patient and a minimum output maintained at 1 to 1.5 liters per twenty-four hours. In addition, 2 Gm. of sodium bicarbonate was administered at 8 a.m., 12 noon, 4 p.m., 8 p.m. and 12 midnight. The amount of free sulfadiazine in the blood was determined by the method of Bratton and Marshall.[7]

Penicillin Therapy.—With but few exceptions, all the patients receiving penicillin were assigned to individual rooms in a "penicillin ward," with specially instructed nursing personnel in charge. The sodium salt of penicillin was used. All the solutions of penicillin were freshly prepared by a member of the Commission. As will be pointed out later, a few of the patients received penicillin intravenously by the continuous drip method. Most of the patients were given the material intermittently by the intramuscular route. Individual doses in 1 to 2 cc. of isotonic solution of sodium chloride were injected into the deltoid muscles or the buttocks. The dosage schedules will be detailed shortly. The patients were examined at least twice daily by one member of the Commission and, independently, once a day by a second member. Materials for culture from the nose and throat were obtained daily during the period of therapy and for one week after. A total of 1,139 cultures were examined in patients receiving penicillin.

Penicillin Therapy Combined with Sulfadiazine Therapy.—A group of patients observed in the manner just described were given four intramuscular injections of penicillin, and then, at the time of the last dose of penicillin, therapy with sulfadiazine was started as previously detailed. Treatment with sulfadiazine was continued for four to five days.

Control Group of Patients.—In order to get more precise information concerning the value of specific therapy, a control group of 102 patients having nasopharyngitis or tonsillitis due to hemolytic streptococci were observed. The absence of a large number of patients with scarlet fever militated against a series of untreated controls. The control patients did not receive salicylates, sulfadiazine or penicillin.

It became apparent early in the course of this investigation that the severity of an infection was an important factor in evaluating any therapeutic agent. Therefore, patients falling into either the control or the treated group were divided into three categories. Patients with mild infections had temperatures below 101 F. The throats showed only mild inflammation, slight edema and exudate, and there was a minimum of associated cervical adenitis. There was little systemic reaction to the infections in that the patients ate well and after a good night of sleep were anxious to be out of bed. Patients with moderate infections had temperatures above 101 F. The inflammatory reaction of the throat induced difficulty in swallowing, and all the patients had an associated cervical adenitis. Systemic reactions included headache, dizziness and loss of appetite. The patients had little desire to be out of bed at the end of the first twenty-four hours of hospitalization. Patients with severe infections were febrile, often complaining of chills or chilly sensations. The edema and exudate of the pharynx were pronounced,

7. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537 (May) 1939.

making swallowing of liquids extremely painful. Many of these patients had had emeses and diarrhea. They complained of having severe headaches. There was no inclination to eat. During the first day or two of hospitalization, they were prostrated. The number of patients in each group on the basis of this classification is shown in table 1. The bacteriologic data for 102 patients are presented in table 2. In this particular series of patients, types 19 and 36 of group A hemolytic streptococci appeared to predominate. Although the number of cases is small, no instance of severe tonsillitis or nasopharyngitis was found to be due to other than group A hemolytic streptococci. Rarely was more than one type of group A hemolytic streptococcus isolated from patients with an acute illness. On the other hand, carriers of hemolytic streptococci frequently may harbor two or more types in the pharynx.

In the main, the clinical course of the patients with acute tonsillitis followed a fairly uniform pattern. At the end of four to five days of

TABLE 1.—*Distribution of Control Patients According to Severity of Infections*

		Number of Patients
Tonsillitis.....		58
Mild.....	12	
Moderate.....	36	
Severe.....	10	
Nasopharyngitis.....		44
Mild.....	18	
Moderate.....	18	
Severe.....	8	
Total.....		102

illness, the temperature approached or became normal. Subjectively, in the cases of more severe illness, the toxemia and sore throat began to abate by the end of forty-eight hours. There was a return of appetite at the same time. Objectively, the edema and exudate began to subside at the end of forty-eight hours of illness. Redness of the throat and adenitis were the last signs to disappear. The redness of the throat frequently persisted after the temperature had remained normal for several days. Likewise, the cervical lymph nodes could not be palpated without some degree of pain being elicited well after the temperature had become normal. The temperature curves and the causative organisms in representative cases of severe tonsillitis are depicted in chart 1. While the majority of patients were enabled to leave the hospital a week after the onset of their illness, they were kept under observation for an additional week in most instances for further bacteriologic and immunologic studies. Suppurative complications were rarely encountered. Cervical adenitis was considered to be a manifestation of acute tonsillitis rather than a complication. Essentially the

TABLE 2.—*Group and Type of Hemolytic Streptococci in Control Patients with Tonsillitis and Nasopharyngitis*

	Types of Group A (Lancefield) Hemolytic Streptococci																	Unable to Type	Group B	Group C	Group G
	3	5	6	9	14	17	18	19	22	26	29	30	36	40	41	44	46				
Tonsillitis																					
Mild..........	1	..	..	..	..	..	..	3	1	..	1	..	1	..	1	..	..	2	1	1	..
Moderate......	..	..	1	..	1	1	1	5	..	1	..	1	12	..	..	1	..	8	..	2	2
Severe.........	2	..	..	..	..	1	..	2	..	..	..	..	3	..	..	2	..	..	..	..	..
Nasopharyngitis																					
Mild..........	1	1	..	1	1	..	..	3	..	..	..	2	..	..	1	1	1	2	..	3	1
Moderate......	1	..	2	..	1	1	..	2	..	..	..	..	3	1	..	2	1	1	..	2	1
Severe.........	3	..	..	..	..	..	..	2	..	..	..	..	..	..	..	1	..	2	..	..	..

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same clinical course was observed in the patients with severe naso-pharyngitis. The temperature curves and the bacteriologic results of typical cases are illustrated in chart 2.

Bacteriologic studies on untreated patients with tonsillitis of all grades of severity showed that two to three weeks after the onset of illness 70 to 75 per cent of the patients still had cultures showing the presence of hemolytic streptococci in the throat, usually of the same
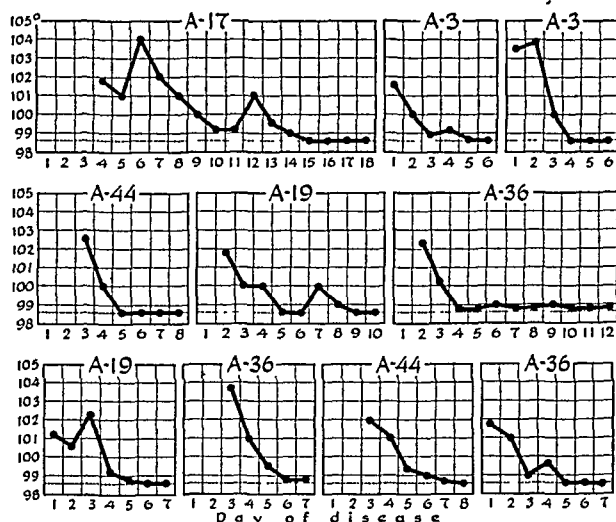
Chart 1.—Composite chart showing temperature curves and types of hemolytic streptococci for 10 patients with severe tonsillitis receiving no specific therapy.
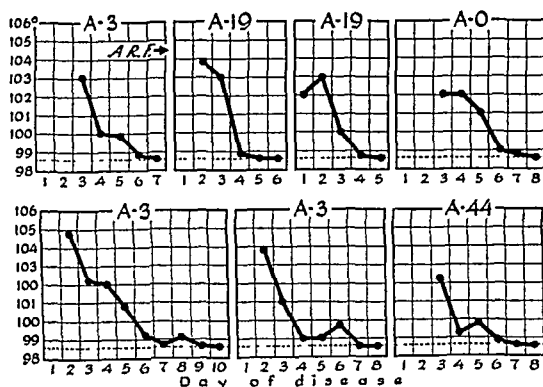
Chart 2.—Composite chart showing temperature curves and types of hemolytic streptococci for 7 patients with severe nasopharyngitis receiving no specific therapy. Note that in 1 patient acute rheumatic fever subsequently developed.

type as isolated on entry to the hospital. This also applied to patients having nasopharyngitis. On the other hand, at the end of this time, there was a pronounced reduction in the incidence of positive cultures of material from the nose. Only approximately 20 to 30 per cent of the

patients continued to have hemolytic streptococci in the nose. Recent evidence accumulated by Hamburger and his group[8] seem to indicate that persons with positive cultures of material from the nose are potentially more dangerous as carriers than those with positive cultures of material from the throat.

EVALUATION OF SULFADIAZINE

The sulfonamide drugs have been used extensively for the treatment of sore throat. The usual method employed is the ingestion of tablets according to various dosage schedules. Another form of therapy is to apply the powder to the pharynx with an atomizer, and, more recently, the use of chewing gum containing a sulfonamide compound has been advocated.

While only 19 patients received sulfadiazine, all were classified as having severe illness. There were 13 with tonsillitis and 6 with nasopharyngitis. Group A hemolytic streptococci were the cause of illness in all cases. Following the dosage schedule previously outlined, the patients received an average of 25 Gm. of sulfadiazine in an average period of five days. In these circumstances, the concentration of free sulfadiazine in the blood varied between 5 and 10 mg. per hundred cubic centimeters. No toxic reactions of any concern were observed. Careful observation of these patients compared with a similar but untreated control group showed that the clinical course of the persons receiving sulfadiazine was altered in one important respect, and that was that the severity of the symptoms abated earlier. The edema of the throat and the exquisite soreness often subsided greatly twelve to eighteen hours after therapy with sulfadiazine was instituted. On the other hand, the duration of the clinical course as a whole was not shortened in the treated group, and therefore the period of hospitalization for the acute illness was the same in the two groups. No conclusions can be drawn concerning the incidence of suppurative complications in the treated group, since complications were uncommon in the untreated patients. It was apparent that sulfadiazine did not reduce the incidence of carriers of hemolytic streptococci. It is of interest that 1 patient having tonsillitis due to group A type 26 hemolytic streptococci was given an initial dose of 3 Gm. of sulfadiazine and then 3 Gm. every three hours, for a total dose of 54 Gm. A 4 plus culture of type 26 hemolytic streptococci was obtained from the throat after therapy had been discontinued.

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8. Hamburger, M., Jr.: Studies on the Transmission of Hemolytic Streptococcus Infections: II. Beta Hemolytic Streptococci in the Saliva of Persons with Positive Throat Cultures, J. Infect. Dis. **75**:71 (July-Aug.) 1944.

EVALUATION OF PENICILLIN

A total of 95 patients received penicillin. Six of the patients had acute rheumatic fever, and the results obtained in this group are reported elsewhere.[9] Of the remaining 89 patients, the conditions treated are shown in table 3. It is to be noted that two groups of patients received penicillin and sulfadiazine. It is generally agreed that group A hemolytic streptococci are sensitive to the antibacterial action of penicillin. An attempt was made to determine the minimal doses of penicillin which would alter the clinical course of the disease and also reduce the incidence of postinfection carriers of hemolytic streptococci.

Treatment of Carriers of Hemolytic Streptococci with Penicillin.— An important factor in the dissemination of hemolytic streptococci is the healthy carrier of group A strains and persons recovering from

TABLE 3.—*Types of Conditions in Eighty-Nine Patients Treated with Penicillin or Penicillin and Sulfadiazine*

		Number of Patients
Penicillin		60
Carriers of hemolytic streptococci	10	
Tonsillitis	30	
Nasopharyngitis	9	
Miscellaneous (infections of the upper respiratory tract of nonstreptococcic origin)	8	
Scarlet fever	2	
Erysipelas	1	
Penicillin and sulfadiazine		29
Scarlet fever	13	
Tonsillitis	16	
Total		89

streptococcic infections. Therefore, a group of 10 persons convalescing from various types of group A hemolytic streptococcus infections were treated with penicillin according to different dosage schedules. Pertinent data regarding the treatment of these patients and the results are presented in table 4. The total dose of sodium penicillin varied between 100,000 and 300,000 units. These relatively small doses were selected for evaluation because the use of larger doses would be impractical in most circumstances. The results indicate that the doses used did not eradicate hemolytic streptococci from the throats. The number of patients who had negative cultures of material from the nose is too small from which to draw any conclusions.

Treatment of Tonsillitis Due to Hemolytic Streptococci with Penicillin.—A group of 30 patients with moderate to severe tonsillitis were given varying doses of sodium penicillin, ranging from 75,000 to 1,000,000

9. Rantz, L. A.; Spink, W. W.; Boisvert, P., and Coggeshall, H.: The Treatment of Rheumatic Fever with Penicillin, J. Pediat. **26**:576 (June) 1945.

TABLE 4.—*Effect of Penicillin on "Carrier State" in Patients Convalescing from Group A Hemolytic Streptococcus Infections*

Initial Streptococcic Disease	Total Dose of Penicillin in Units and Method of Administration	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture			
		Before Penicillin		After Penicillin	
		Nose	Throat	Nose	Throat
Nasopharyngitis	100,000 as continuous intravenous drip in 10 hr.	Type 0,* 4+	Type 0,* 2+	Negative	Type 0, 1+
Nasopharyngitis	100,000 as continuous intravenous drip in 10 hr.	....	Type 19, 3+	....	Type 19, 3+
Tonsillitis	100,000 as continuous intravenous drip in 10 hr.	Type 17, 1+	Type 17, 3+	Negative	Type 17, 3+
Tonsillitis	100,000 as continuous intravenous drip in 10 hr.	Type 36, 2+	Type 36, 3+	Negative	Type 36, 4+
Nasopharyngitis	200,000—25,000 every 6 hr. × 8, intramuscularly	Type 0,* 4+	Type 0,* 3+	Negative	Group G, 1+
Tonsillitis	200,000—25,000 every. 6 hr. × 8, intramuscularly	Type 19, 4+	Type 19, 4+	Type 19, 1+	Type 19, 1+
Nasopharyngitis	200,000—25,000 every 4 hr. × 8, intramuscularly	Type 19, 4+	Type 19, 2+	Negative	Type 19, 1+
Convalescent from scarlet fever	300,000—25,000 every 6 hr. × 12, intramuscularly	....	Type 17, 2+	....	Group B, 3+; Group G, 3+
Convalescent from scarlet fever	300,000—25,000 every 6 hr. × 12, intramuscularly	....	Type 17, 4+	Type 17, 3+	Type 17, 1+
Convalescent from scarlet fever	100,000—50,000 every 7 hr. × 2, intramuscularly	Negative	Type 19, 2+	Type 19, 4+	Type 19, 1+

* Type 0 = unable to type.

units. Data pertaining to the doses used, the bacteriologic observations and the clinical results are given in table 5. The effect of the penicillin on the clinical course of the patients was variable with 1 exception. Within eight to twelve hours after the beginning of therapy the majority of patients looked and felt better. This applied to patients who received 25,000 units intramuscularly every four hours for eight
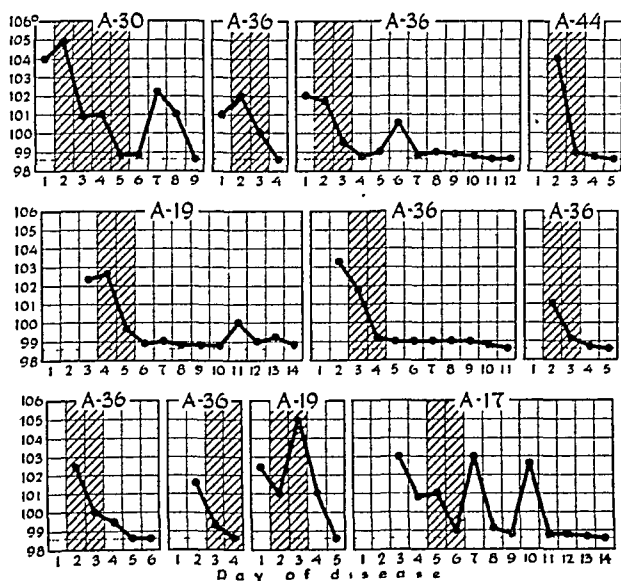
Chart 3.—Composite chart showing temperature curves and types of hemolytic streptococci for 11 patients with severe tonsillitis who received penicillin. Hatched areas indicate periods during which penicillin was given.
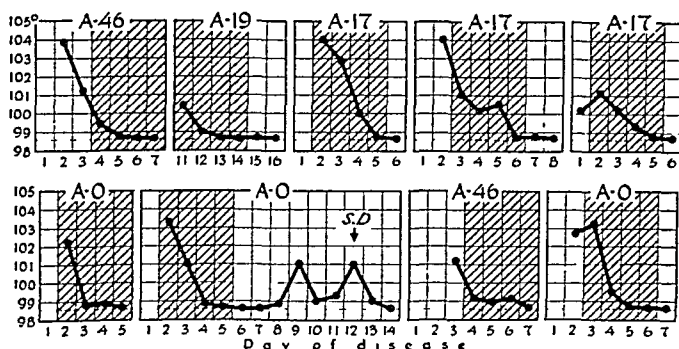
Chart 4.—Composite chart showing temperature curves and types of hemolytic streptococci for 9 patients with severe tonsillitis who received penicillin. Hatched areas indicate periods during which penicillin was given.

doses, for a total of 200,000 units, as well as patients who received a total of 1,000,000 units. With possibly 1 exception, the patients tolerated the penicillin well. In patient 9 a generalized urticaria developed the seventh and eighth days after therapy, when penicillin was discontinued. This was assumed to be due to penicillin, since other possible causes appeared to be ruled out. Charts 3 and 4 present

TABLE 5.—*Effect of Penicillin Administered Intramuscularly on the Clinical Course and Bacteriologic Status of Patients Having Tonsillitis Due to Hemolytic Streptococci*

Total Dose of Penicillin in Units and Method of Administration	Interval Between Initial Treatment and Normal Temperature	Before Penicillin Nose	Before Penicillin Throat	After Penicillin Nose	After Penicillin Throat	Comments
75,000—15,000 every 4 hr. × 5	24 hr.	Negative	Group C, 3+	Negative	Group B, 1+	Within 24 hr. reinfection with group B
150,000—25,000 every 4 hr. × 8	48 hr.	Negative	Type 36, 4+	Type 36, 1+	Type 36, 4+	Good response
200,000—25,000 every 4 hr. × 8	24 hr.	Negative	Type 36, 4+	Negative	Type 36, 4+	Peritonsillar abscess ruptured during therapy
200,000—25,000 every 4 hr. × 8	12 hr.	....	Group G, 1+	Negative	Negative	Good response
200,000—25,000 every 4 hr. × 8	48 hr.	Type 36, 4+	Type 36, 3+	Type 36, 4+	Type 36, 3+	Clinical relapse
200,000—25,000 every 4 hr. × 8	12 hr.	Type 36, 4+	Type 36, 3+	Type 36, 4+	Type 36, 3+	Herpes simplex
200,000—25,000 every 4 hr. × 8	12 hr.	Type 36, 4+	Type 36, 4+	Type 36, 4+	Type 36, 3+	72 hr. after therapy, anorexia and headache
200,000—25,000 every 4 hr. × 8	48 hr.	Negative	Type 36, 3+	Type 36, 1+	Type 36, 3+	Urticaria 7 and 8 days after therapy; "head cold"
200,000—25,000 every 4 hr. × 8	8 days	Negative	Type 36, 4+	Type 0,* 3+	Type 36, 4+	Good response with penicillin; febrile "Head cold" with penicillin; temperature 101.5 F. day after relapse, temperature discontinued, with penicillin therapy due to rupture of drum membrane due to otitis media; controlled with sulfadiazine
200,000—25,000, as intravenous drip; 300,000—100,000, as intravenous drip; 200,000—25,000 every 4 hr. × 8	12 hr.; 4 days	Type 44, 1+; Type 17, 3+	Type 44, 4+; Type 17, 4+	Negative; Type 17, 4+	Type 44, 3+; Type 17, 4+	Received 12 Gm. sulfadiazine without effect; good response to first course of penicillin; reinfection with type 36; good response to second course of penicillin
(1) 300,000—25,000 every 4 hr. × 12	24 hr.	Type 19, 4+	Type 19, 4+	Type 36, 3+	Type 36, 3+	—
(2) 200,000—25,000 every 4 hr. × 8						
400,000—50,000 every 4 hr. × 8	6 days	Type 17, 4+	Type 17, 4+	Negative	Type 17, 3+	Fair response
400,000—25,000 every 4 hr. × 16	6 days	Type 0,* 2+	Type 0,* 4+	Negative	Type 0,* 1+	Slow response
400,000—25,000 every 6 hr. × 16	5 days	Type 36, 2+	Type 36, 4+	Negative	Type 36, 3+	Severe clinical relapse 48 hr. after therapy; acute rheumatic fever
400,000—50,000 every 6 hr. × 8	24 hr.	Type 0,* 2+	Type 0,* 4+	Negative	Type 0,* 4+	Herpes simplex
400,000—50,000 every 6 hr. × 8; 4; 25,000	13 days	Type 19, 4+	Type 19, 4+	Negative	Type 19, 4+	Fair response
400,000—50,000 every 4 hr. × 8	7 days	Negative	Type 3, 3+	Negative	Negative	Fair response
100,000—50,000 every 6 hr. × 8; 2; 25,000 every 6 hr. × 4; 2; 25,000 every 4 hr.; 150,000—60,000 every 4 hr. × 4; 15,000 every 4 hr. × 10	5 days	Negative	Type 3, 4+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20	48 hr.	Negative	Type 46, 3+	Type 46, 1+	Type 46, 1+	Good response
500,000—25,000 every 4 hr. × 20	96 hr.	Type 19, 4+	Type 19, 4+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20	48 hr.	....	Type 36, 3+	Negative	Negative	Herpes simplex
500,000—25,000 every 4 hr. × 20	96 hr.	Negative	Type 0,* 4+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20	96 hr.	Negative	Type 17, 1+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20	6 days	Negative	Group G, 4+	Negative	Negative	Good response
1,000,000—50,000 every 4 hr. × 20	72 hr.	Negative	Type 0,* 1+	Negative	Type 0,* 3+	Fever, 7 days after therapy; acute rheumatic fever temperature 101 F.
1,000,000—50,000 every 4 hr. × 20	24 hr.	Type 0,* 4+	Type 0,* 4+	Type 0,* 3+	Type 0,* 4+	5 days after therapy, temperature 101 F. recovery after sulfadiazine
1,000,000—50,000 every 4 hr. × 20	24 hr.	Type 19, 4+	Type 19, 4+	Negative	Negative	Slight clinical relapse
1,000,000—50,000 every 4 hr. × 20	24 hr.	Type 46, 4+	Type 46, 3+	Negative	Negative	Good response

* Type 0 = unable to type.

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composite data for 20 patients who received varying doses of peni-
cillin. If one compares the temperature curves of the untreated control
group (chart 1) with the curves of the treated group (chart 3), it is
to be noted that there is little difference in the time in which the
temperatures become normal. Objectively, the throats of the treated
group did not manifest any abrupt clearing of the exudate and redness
when compared with the control group. The edema of the pharynx
and tonsils and the cervical adenitis of patients receiving penicillin
did appear to recede more rapidly than that of those in the untreated
group. The outstanding difference between the two groups as already
cited was that the treated persons felt better sooner than the patients
who did not receive penicillin.

There were 6 persons (patients 6, 8, 12, 22, 23 and 24) who had
clinical relapses following the cessation of therapy with penicillin. In
5 of the 6 patients, this was associated with a bacteriologic relapse.
The relapses did not appear to be related to the total dose of penicillin
administered. The significance of these postpenicillin relapses will be
commented on shortly. Acute rheumatic fever developed in 2 persons
(patients 12 and 22) as a sequel to their streptococcic infections.

The effect of penicillin on the presence of hemolytic streptococci in
the noses and throats of these patients is of considerable significance.
Materials for culture from the nose and throat were obtained from
the patients every day during the course of treatment and for at least
one week thereafter. When a total dose of 200,000 units was admin-
istered, hemolytic streptococci were frequently absent from cultures
during the period of therapy. However, with this dose, streptococci
of the same type usually reappeared in the cultures immediately after
the cessation of therapy. When a total dose of 400,000 to 500,000
units was given, streptococci again were absent from cultures. After
treatment was discontinued the cultures of material from the throat
became positive but the cultures of material from the nose remained
free of streptococci. In other words, it would appear that such doses
eradicated streptococci from the nose but not from the throat. When
500,000 to 1,000,000 units of penicillin were administered, the majority
of patients showed an absence of hemolytic streptococci in the nose
and throat during and after therapy. Nevertheless, in 2 patients
(patients 23 and 24) who received 1,000,000 units, group A hemo-
lytic streptococci persisted in the nose and throat of 1 and in the throat
of the other after therapy had been discontinued.

The advantages and disadvantages of therapy with penicillin may be
further illustrated by a discussion of the following cases.

CASE 1.—A 32 year old white man entered the station hospital on Feb. 15,
1944. Two days previously he had had chills, fever, severe sore throat, headache
and generalized malaise. On entry, the tonsils were massively enlarged, meeting

in the midline, and greatly inflamed, with exudate present in the crypts. He was seriously ill, and on the second day in the hospital therapy with sulfadiazine was started. The patient received a total of 12 Gm. in three days. The level of free sulfadiazine in the blood was 10.44 mg. per hundred cubic centimeters. This treatment was without demonstrable benefit. A consultant stated that the patient had an early peritonsillar abscess on the left associated with pronounced left cervical adenitis. At this time he was given 25,000 units of sodium penicillin intramuscularly every four hours for twelve doses, or a total of 300,000 units in three days.
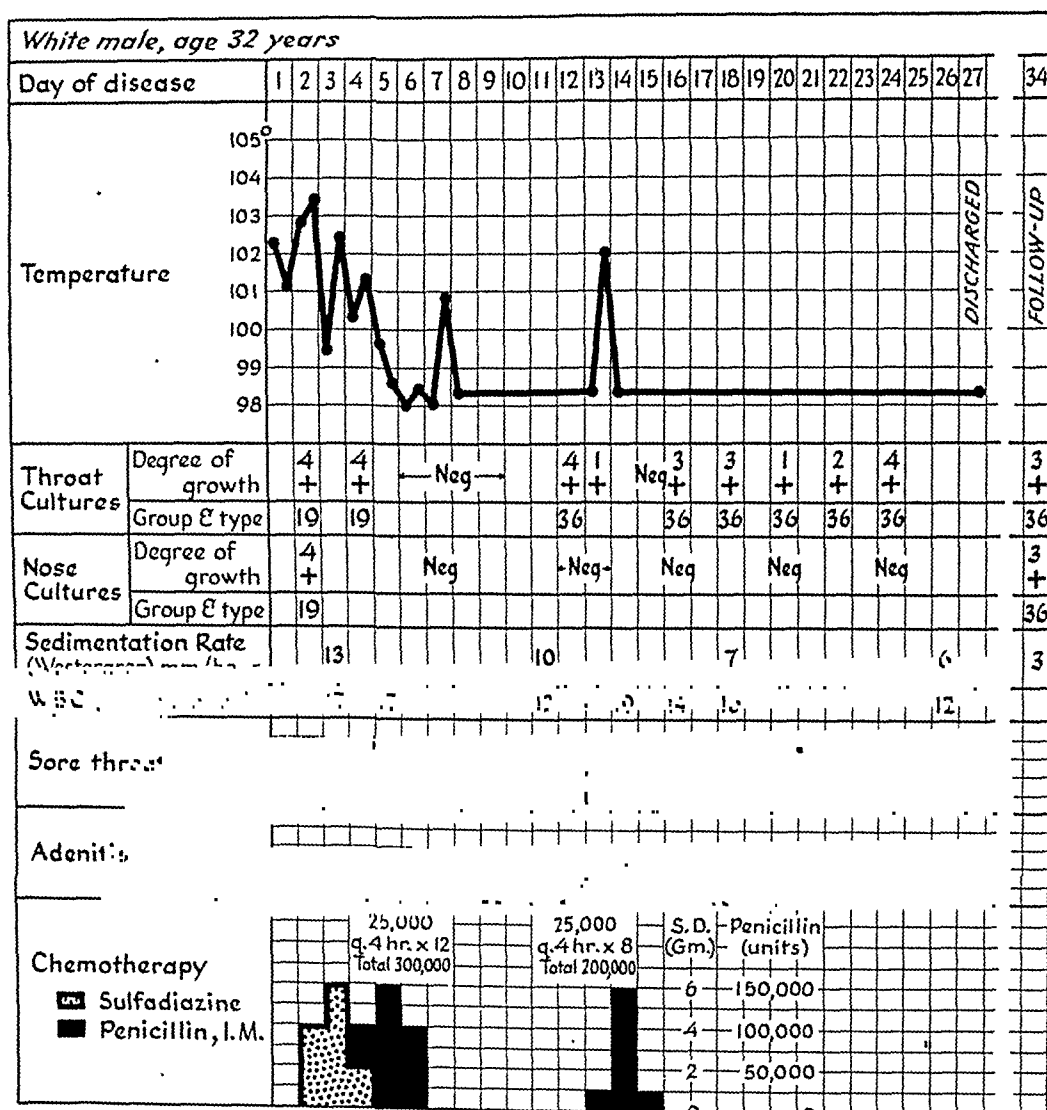
Chart 5.—Effect of penicillin on the clinical course of a severe tonsillitis. Note that sulfadiazine failed to affect the clinical course but a prompt response with penicillin was obtained.

This procedure resulted in prompt improvement. On the third day of treatment there was no adenitis and the peritonsillar swelling had subsided. The day after penicillin had been discontinued the patient had a febrile reaction of 101.6 F. but no other complaints. Seven days after therapy with penicillin he had a remission of his symptoms. This probably represented a hospital reinfection, since on the initial cultures were group A type 19 streptococci and this relapse was associated with

group A type 36 organisms. Penicillin was again administered intramuscularly in doses of 25,000 units every four hours for eight doses, or a total of 200,000 units. There was prompt improvement, but the type 36 streptococci were only temporarily eradicated from the throat. The patient's clinical course is illustrated in chart 5.

Comment: This patient was definitely benefited by penicillin on two occasions. Although the first course of penicillin resulted in prompt improvement, he had a temporary febrile relapse on the day following the completion of therapy. This phenomenon was observed in several patients receiving penicillin. The second course of therapy was given for a reinfection and resulted in clinical improvement, but hemolytic streptococci were not eradicated from the pharynx.

CASE 2.—A 36 year old white man entered the station hospital on Feb. 21, 1944. He had had hoarseness and a nonproductive cough for one week. His illness was mild, and he was afebrile. Although group A type 30 streptococci were isolated from his throat, there existed the possibility that he had a nonstreptococcic, "viral" infection of the upper part of the respiratory tract and that he was a carrier of type 30 organisms. On the ninth day in the hospital he became febrile and generalized aches and pains and a headache developed. The following day he became extremely ill, with a severe sore throat, enlarged and reddened tonsils, pronounced edema and exudate of the left tonsil and moderately severe bilateral cervical adenitis. The next day his condition was worse, with evidence of an early peritonsillar abscess present on the left. Type 36 streptococci were cultured from materials from the nose and throat. This indicated a hospital infection. He was given sodium penicillin intramuscularly, receiving 25,000 units every four hours for sixteen doses, or a total of 400,000 units. Coincident with this therapy there was prompt and progressive improvement in his condition. At the conclusion of therapy, on the fourth day, the throat was only slightly sore, but exudate was still present on the left tonsil and the left cervical adenitis persisted. Forty-eight hours after the discontinuation of penicillin therapy, he had a relapse, with fever and a sore throat. No specific treatment was instituted, and he became afebrile in two days. Subsequently, acute rheumatic fever developed. His clinical course is graphically shown in chart 6.

Comment: The patient had severe acute tonsillitis, but his initial response to penicillin was satisfactory. He suffered a clinical and bacteriologic relapse due to the same type of hemolytic streptococci, but the symptoms subsided without specific therapy. His convalescence was complicated by the onset of acute rheumatic fever.

CASE 3.—A 19 year old white youth entered the station hospital because of a sore throat and slight fever of one day's duration. He had an injected pharynx, with enlarged red tonsils having exudate in the follicles. Group C hemolytic streptococci were isolated from the throat. His course was benign, but the day before he left the hospital group A type 17 streptococci were obtained in a culture of material from the throat. On the day of discharge he felt feverish and his throat was sore. The following day he was readmitted to the hospital because of a severe sore throat and a temperature of 102.5 F. The tonsils were extremely enlarged and reddened, and considerable exudate was present on each tonsil. He also had a severe degree of cervical adenitis. Type 17 streptococci were again

found in cultures of material from the throat. On his second day in the hospital he was given 100,000 units of penicillin in 1 liter of isotonic solution of sodium chloride as an intravenous drip. Although his temperature dropped and no hemolytic streptococci were obtained from a culture of material from the throat, his general condition had not changed much for the better. Shortly after receiving
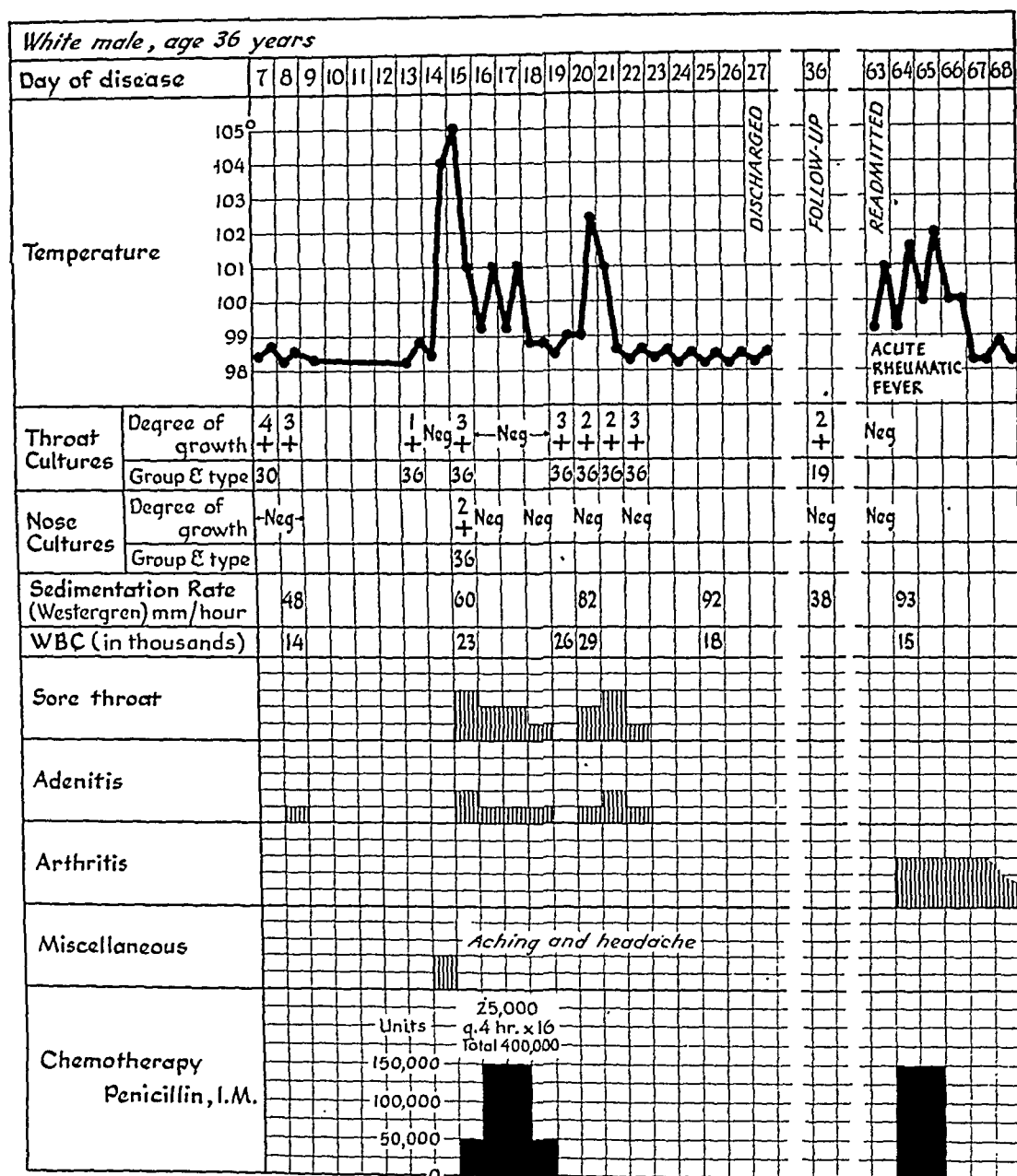
Chart 6.—Effect of penicillin on clinical course of severe tonsillitis. Note the bacteriologic and clinical relapse after 400,000 units had been given. Acute rheumatic fever developed in the patient, which was controlled with a salicylate.

the penicillin, he complained of pain in the right ear; examination revealed a red tympanic membrane but not one that was bulging. That evening he had a severe sore throat; he was unable to swallow, and his ear ached considerably. On the following day the ear had stopped aching, the tonsils did not appear so edematous.

his throat was still sore and the adenitis was less pronounced, but the exudate on the tonsils was just as prominent. He was then given an additional 200,000 units of penicillin intramuscularly in seven divided doses. After the therapy, he felt much better. He was afebrile, the adenitis was diminished and the edema, redness and exudate of the tonsils had receded about 50 per cent. He continued to improve, but on the day following the discontinuation of penicillin he complained of the symptoms of a "head cold." Simultaneously, type 17 hemolytic streptococci reappeared in his pharynx. Six days following therapy with penicillin, his tonsils
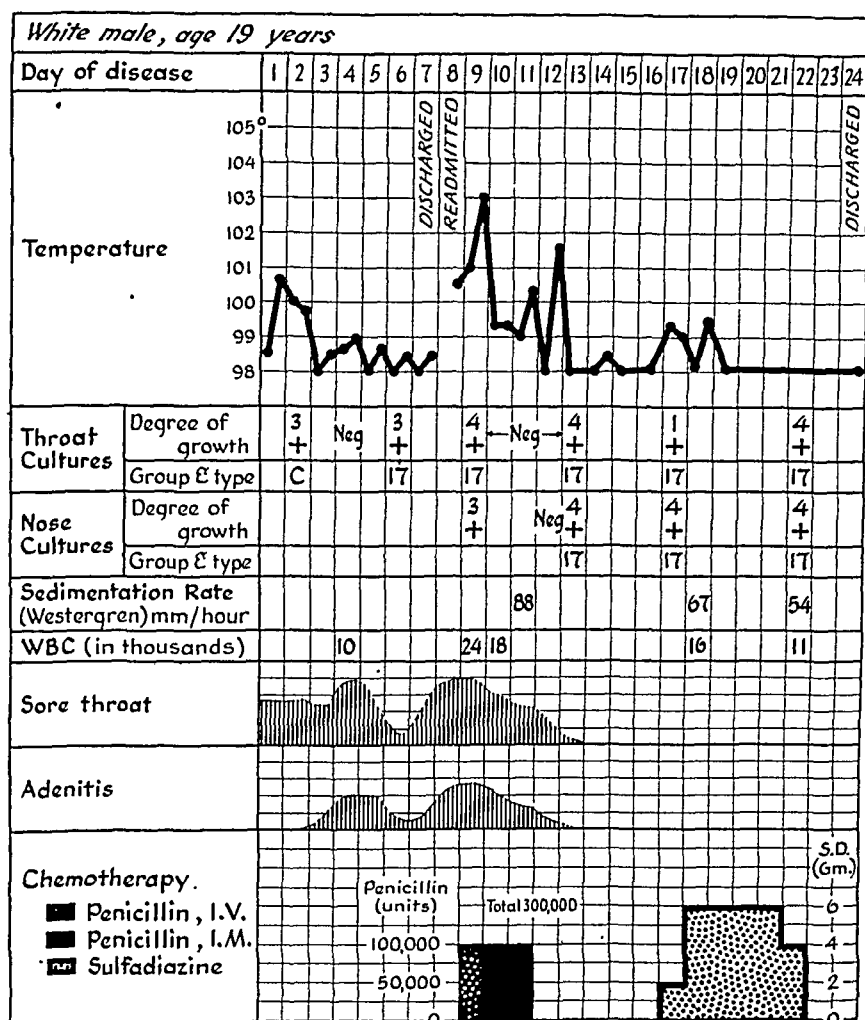
Chart 7.—Effect of penicillin on severe tonsillitis. Clinical and bacteriologic relapse occurred. Otitis media was controlled with sulfadiazine.

were decidedly injected, with a reappearance of exudate and edema. He also complained of a throbbing pain in his right ear, and the tympanic membrane was reddened but not bulging. During the night the membrane of his ear drum ruptured spontaneously, and a serosanguineous discharge was present. Group G streptococci were cultured from this material. He was then given sulfadiazine for the next five days, receiving a total of 30 Gm. Under this regimen, the aural discharge disappeared, and he made an uneventful recovery. When he left the

hospital, group A type 17 streptococci were still present in the nose and throat. Chart 7 illustrates the clinical course and the treatment of this patient.

Comment: This patient had clinical relapses after each of two courses of penicillin. Otitis media was not completely controlled with penicillin, but it abated after spontaneous drainage and the use of
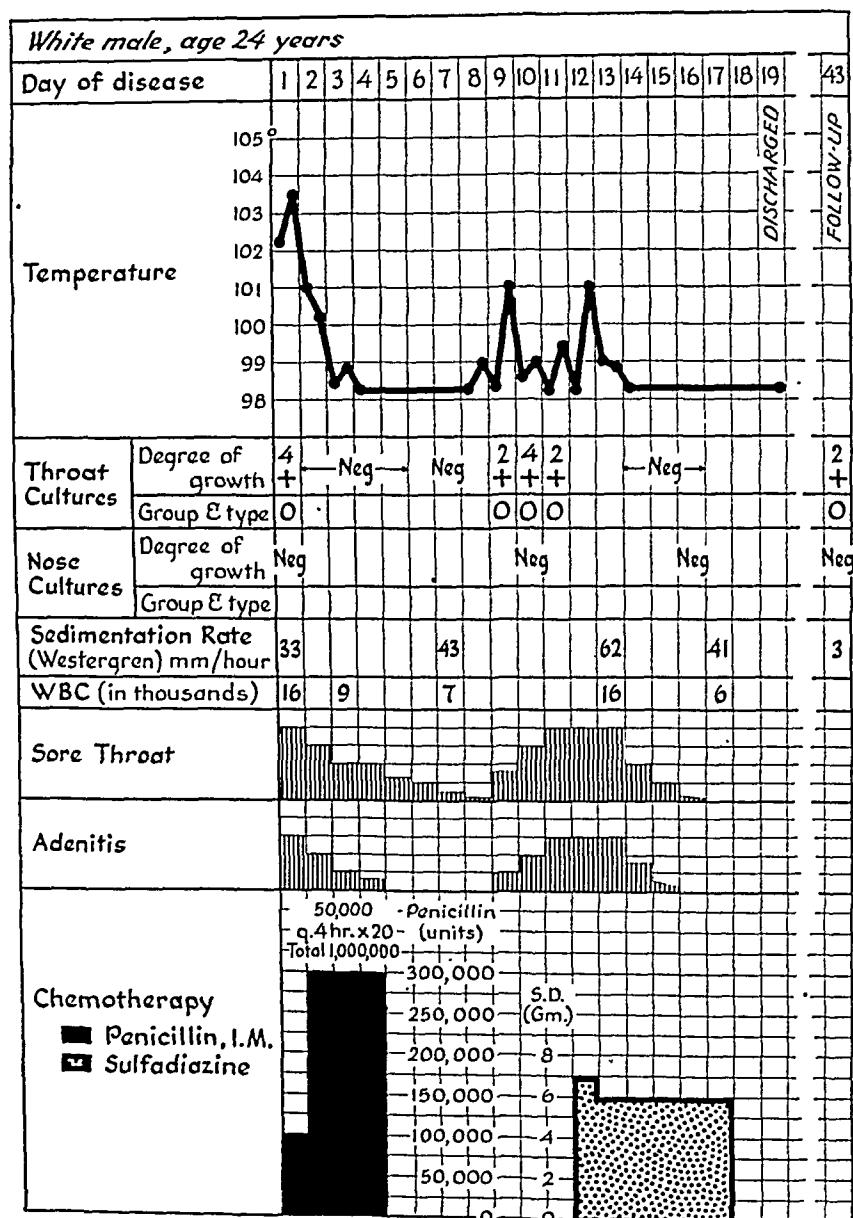
Chart 8.—Effect of 1,000,000 units on severe tonsillitis. Note the clinical and bacteriologic relapse, which subsided when sulfadiazine was administered. 0 indicates that we were unable to type the organisms.

sulfadiazine. The patient also had a bacteriologic relapse with type 17 streptococci.

CASE 4.—A 24 year old white man entered the station hospital on March 16, 1944. The day before entry he had an onset of chills, headache and severe malaise.

TABLE 6.—*Effect of Penicillin Administered Intramuscularly on the Clinical Course and Bacteriologic Status of Patients Having Nasopharyngitis Due to Hemolytic Streptococci*

Total Dose of Penicillin in Units, and Method of Administration	Interval Between Initial Treatment and Normal Temperature	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture				Comments
		Before Penicillin		After Penicillin		
		Nose	Throat	Nose	Throat	
200,000—25,000 every 4 hr. × 8............	12 days	Type 0,* 2+	Type 0,* 3+	Type 0,* 1+	Type 0,* 4+	Temperature 102 F., 5h day after therapy
200,000—25,000 every 4 hr. × 8............	24 hr.	Type 36, 3+	Type 36, 3+	Negative	Type 36, 3+	Fever 24 hr. after therapy, persisting for 17 days; responded to sulfadiazine; then atypical pneumonia
200,000—50,000 every 6 hr. × 4............	48 hr.	Negative	Type 0,* 3+	Negative	Negative	Good response
300,000—37,500 every 4 hr. × 8............	24 hr.	Negative	Type 0,* 2+	Negative	Type 0,* 3+	48 hr. after therapy, temperature 101.4 F.; normal in 96 hr.
400,000—50,000 every 4 hr. × 8............	36 hr.	Type 13 and 28, 2+	Type 13 and 28, 3+	Negative	Type 13 and 28, 3+	48 hr. after therapy, temperature 99.2 F., with slight adenitis
500,000—25,000 every 4 hr. × 20............	72 hr.	Type 12, 3+	Type 12, 3+	Negative	Type 12, 3+	Fair response
500,000—25,000 every 4 hr. × 20............	24 hr.	Negative	Group B, 3+	Negative	Type 0,* 3+	Clinical relapse due to reinfection with another type
500,000—25,000 every 4 hr. × 20............	48 hr.	Type 46, 3+	Type 46, 4+	Negative	Negative	Good response
1,000,000—50,000 every 4 hr. × 20............	24 hr.	Type 46, 3+	Type 46, 3+	Negative	Type 46, 3+	72 hr. after therapy temperature 102 F.

* Type 0 = unable to type.

On entry, he appeared rather toxic. His pharynx and tonsils were extremely reddened and edematous, with considerable exudate on the left tonsil. A severe bilateral cervical adenitis was present. While group A streptococci were obtained from a culture of material from the throat, typing of this strain was unsuccessful. He was given 1,000,000 units of penicillin intramuscularly in doses of 50,000 units administered every four hours twenty times. On the second day of therapy he felt much better, although his throat and the adenitis appeared essentially the same. However, from then on there was subjective and objective improvement. Three days after the cessation of therapy his pharynx and tonsils appeared normal and he had no complaints. Five days after therapy he had fever, with headache, sore throat and redness and edema of the throat. He also had a bacteriologic relapse. He was then given a total of 19 Gm. of sulfadiazine in a period of three days, which was associated with progressive improvement. Hemolytic streptococci disappeared from the throat while sulfadiazine was being administered. Chart 8 illustrates the clinical course of this patient.

Comment: A patient with severe tonsillitis was given 1,000,000 units of penicillin, which was associated with progressive improvement. However, five days after the completion of therapy, he had a clinical relapse and sulfadiazine was administered. He then made an uneventful recovery.

Treatment of Nasopharyngitis Due to Hemolytic Streptococci with Penicillin.—A group of 9 patients having a severe form of nasopharyngitis due to hemolytic streptococci were treated with intramuscular injections of sodium penicillin. The total doses of penicillin varied between 200,000 and 1,000,000 units. The initial clinical results obtained in this group were essentially the same as those observed in the foregoing patients with tonsillitis. Clinical and bacteriologic data relating to this group of patients are presented in table 6.

While the initial response to penicillin was satisfactory, it is to be noted that 6 of the 9 patients treated had clinical relapses with varying degrees of severity following the discontinuation of therapy with penicillin. In every instance except 1 the clinical relapse was associated with the same type of streptococci which precipitated the original illness. While 8 of the 9 patients had negative cultures of material from the nose when discharged from the hospital, only 2 patients had cultures of material from the throat free of hemolytic streptococci. It is of interest that 1 patient (patient 5) had types 13 and 28 in his nose and throat just before penicillin was administered and after therapy the same two types were present in the culture of material from the throat but absent from that from the nose.

In summing up the advantages and disadvantages of the use of penicillin for tonsillitis and nasopharyngitis of streptococcic origin, one finds the following advantages:

1. The severity of the symptoms appeared to abate more rapidly than did that of the untreated patients or of the group treated with

sulfadiazine. These beneficial effects were observed with as little as 200,000 units given intramuscularly in divided doses.

2. Severe tonsillitis with such complications as early peritonsillar abscess may not respond favorably to sulfadiazine, but desired results may follow the administration of penicillin.

3. Therapy with penicillin was rarely associated with toxic reactions.

The disadvantages of using penicillin for these diseases are as follows:

1. It is necessary to administer the material parenterally in divided doses, which would prove to be impractical in many instances. Penicillin did not prove to be effective in a few cases when a solution of the material was applied locally to the issues with an atomizer at frequent intervals.

2. While doses of 200,000 units provoked a satisfactory clinical response, doses of 500,000 to 1,000,000 units given in divided amounts were necessary before hemolytic streptococci could be considered to be eradicated from the pharynx. Even with these doses, bacteriologic relapses occurred, though during the period of therapy streptococci were absent from cultures of material from the nose and throat. The period over which a total dose of penicillin was administered appeared to be an important factor in eliminating hemolytic streptococci from the pharynx. Thus, multiple small doses given over a period of several days appeared to be more advantageous than the same total dose given in a shorter period. On the other hand, such a procedure was not without considerable discomfort to the patient when as many as twenty intramuscular injections were given.

3. While the initial therapeutic response to penicillin was satisfactory and streptococci were often absent from cultures of material from the nose and throat after the cessation of therapy, several instances of more or less severe clinical relapses were encountered. These relapses were often associated with the reappearance in the throat of the same type of hemolytic streptococci which initiated the illness. Not only did clinical relapses occur, but complications such as otitis media were encountered.

4. Penicillin did not prevent the development of acute rheumatic fever as a sequel to the streptococcic disease for which penicillin was administered.

Treatment of Miscellaneous Infections of the Upper Respiratory Tract of Nonstreptococcic Origin with Penicillin.—During the course of this investigation, a small group of patients with nonstreptococcic infections of the upper respiratory tract were treated with penicillin. These patients were acutely ill when first seen, and the clinical features suggested an infection due to hemolytic streptococci. Therefore, before

the bacteriologic results were known, the patients were given the anticipated benefit of therapy with penicillin. These patients included 3 with tonsillitis and exudate on the tonsils and 4 with nasopharyngitis. Cultures of material from the nose and throat on repeated occasions failed to reveal the presence of hemolytic streptococci. In these circumstances, the clinical effect of penicillin could not be ascertained. Coincident with the administration of 200,000 to 1,000,000 units of penicillin, the patients improved. It is of significance that several of these patients had hoarseness and cervical adenitis was minimal or absent. The latter is uniformly present in patients having tonsillitis and nasopharyngitis of hemolytic streptococcus origin.

One patient with a severe peritonsillar abscess was treated with penicillin. He experienced considerable relief only after spontaneous rupture of the abscess occurred. Cultures of material from the nose and throat obtained before and after therapy failed to reveal the presence of hemolytic streptococci. In fact, aerobic and anaerobic cultures were made with purulent exudate obtained from the site of rupture, and no micro-organisms were recovered. Penicillin did not affect the course of this patient's illness.

Treatment of Erysipelas with Penicillin.—Only 1 patient was treated, and he received 200,000 units. The infection was due to type 44 streptococci. Coincident with therapy begun on the second day of illness, there was progressive improvement. Type 44 streptococci were present in cultures of material from the throat after therapy was completed.

EVALUATION OF PENICILLIN IN COMBINATION WITH SULFADIAZINE

In order to obviate the necessity of giving multiple injections of penicillin for several days, it was decided to give a total amount of 200,000 units of penicillin in divided doses to a group of patients and then to follow this with sulfadiazine. Another reason for considering this therapeutic approach was an attempt to prevent the clinical relapses which were seen after penicillin alone was used. It was noted that although streptococci were not usually eliminated from the throat during or after therapy with sulfadiazine clinical relapses were less frequently encountered. While treatment with penicillin resulted in a more satisfactory initial clinical response and streptococci in the majority of cases were absent from cultures of material from the throat during the period of therapy, the clinical relapses were often associated with the reappearance of streptococci in cultures of material from the throat. The relapses, with a few exceptions, were not severe. The significant observations were fever lasting twenty-four to forty-eight hours, recurrence of a sore throat, reappearance of exudate in some instances and, more commonly, recurrence of edema and redness of the pharynx

and tonsils. That these clinical manifestations were relapses and not reinfections is shown by the fact that the same type of hemolytic streptococci was present in cultures of material from the throat as was found before treatment with penicillin. The significance of these relapses occurring in the group treated with penicillin will be discussed shortly.

Treatment of Tonsillitis with Penicillin Followed by Sulfadiazine.— A group of 14 patients having severe tonsillitis due to group A hemolytic streptococci were first treated with 200,000 units of penicillin, 50,000 units being given intramuscularly every six hours for four doses. At the time of the last injection of penicillin, the patients were given 3 Gm. of sulfadiazine and then 1 Gm. every four hours. The total dose of sulfadiazine, the duration of treatment and the results are shown in table 7.
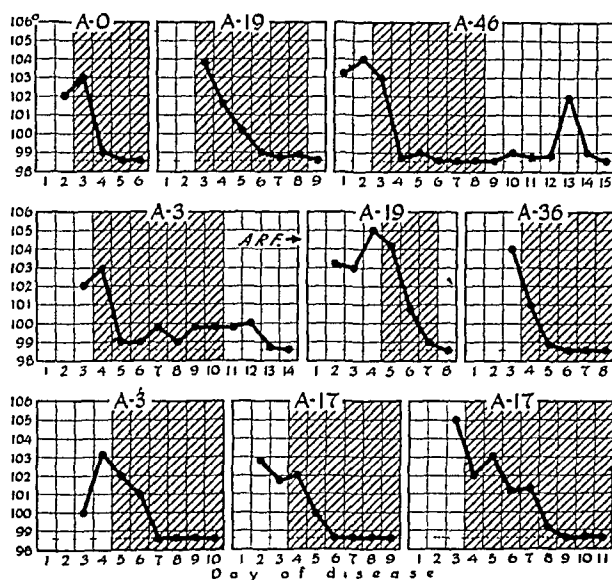
Chart 9.—Composite chart for 9 patients with severe tonsillitis who received 200,000 units of penicillin and then sulfadiazine. Acute rheumatic fever developed in 1 patient. Hatched areas indicate period when penicillin and sulfadiazine were administered. 0 indicates that we were unable to type the organisms.

All the patients tolerated the treatment well except 1 (patient 2), in whom urticaria and hallucinations developed on the second day of therapy with sulfadiazine. It was not known whether this reaction was due to penicillin or to sulfadiazine.

The response of the patients to the treatment was not dramatic, although the severity of the disease appeared to be diminished soon after treatment with penicillin was begun. Chart 9 is a composite chart for 9 patients with severe tonsillitis who received both drugs. The effect of this combined treatment on the streptococci in the nose and throat was of interest in that the majority of the patients had negative cultures while receiving penicillin and sulfadiazine, but when

TABLE 7.—*Effect of Penicillin Administered Intramuscularly and Followed by Sulfadiazine Administered Orally on the Clinical Course and Bacteriologic Status of Patients Having Tonsillitis Due to Hemolytic Streptococci*

Total Dose of Penicillin in Units, and Method of Administration	Total Dose Sulfadiazine	Interval Between Initial Treatment and Normal Temperature	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture				Comments
			Before Treatment		After Treatment		
			Nose	Throat	Nose	Throat	
200,000—50,000 every 6 hr. × 4....	33 Gm. 6 days	11 days	....	....	Negative	Type 3, 3+	Temperature of 100 F. persistent 8 days after treatment started; reinfection type 46, 10 days after sulfadiazine discontinued; 29 days after sulfadiazine, acute rheumatic fever, with type 30 in throat
200,000—50,000 every 6 hr. × 4....	8 Gm. 2 days	48 hr.	Type 19, 4+	Type 19, 4+	Negative	Negative	Good response; sulfadiazine stopped because of urticaria and hallucinations
200,000—50,000 every 6 hr. × 4....	21 Gm. 5 days	48 hr.	Negative	Type 0,* 1+	Negative	Type 0,* 2+	Good response
200,000—50,000 every 6 hr. × 4....	41 Gm. 7 days	96 hr.	Type 17, 4+	Negative	Negative	Type 46, 1+	Fair response; reinfection with another type
200,000—50,000 every 6 hr × 4....	29 Gm. 5 days	6 days	Negative	Type 3, 3+	Negative	Type 3, 4+	Fair response; "head cold" during therapy
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	72 hr.	Type 46, 1+	Type 46, 3+	Negative	Type 46, 4+	5 days after sulfadiazine clinical relapse with temperature 102 F.
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	48 hr.	Negative	Type 3, 3+	Negative	Negative	Good response
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	6 days	Negative	Type 19, 3+	Type 19, 1+	Type 19, 1+	Fair response
200,000—50,000 every 6 hr. × 4....	20 Gm. 4 days	96 hr.	Negative	Type 36, 4+	Negative	Negative	Fair response
200,000—50,000 every 6 hr. × 4....	25 Gm. 5 days	48 hr.	Type 17, 4+	Type 17, 3+	Negative	Type 17, 3+	Good response; acute rheumatic fever developed
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	72 hr.	....	Type 5, 3+	Negative	Type 5, 4+	Fever and tonsillitis 48 hr. after therapy
200,000—50,000 every 4 hr. × 4....	40 Gm. 7 days	5 days	Type 3, 3+	Negative	Negative	Negative	Peritonsillar abscess ruptured during penicillin therapy; culture of exudate sterile
150,000—25,000 every 4 hr. × 6....	26 Gm. 5 days	96 hr.	Type 5, 4+	Type 5, 3+·	Negative	Type 5, 3+	Good response
200,000—50,000 every 8 hr. × 4....	38 Gm. 10 days	14 days	Type 17, 4+	Type 17, 3+	Negative	Type 17, 1+	Otitis media aborted; sinusitis but slightly improved

* Type 0 = unable to type.

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therapy was discontinued there was a reappearance of streptococci in the cultures of material from the throat in all the patients except 3. However, only 1 patient had a positive culture of material from the nose when he left the hospital. Two patients (patients 6 and 11) had bacteriologic and clinical relapses after therapy had been discontinued. One patient (patient 1) had a reinfection with another type of hemolytic streptococcus, and a severe form of acute rheumatic fever developed. A second patient (patient 10) had a bacteriologic relapse and acute rheumatic fever developed.

The following 2 cases illustrate the effect of this type of therapy on the disease:

CASE 1.—A 19 year old white youth entered the station hospital on March 22, 1944. The previous day he had an onset of sore throat, fever, chills and vomiting. He appeared extremely toxic, complaining of a severe sore throat and inability to eat. The pharynx was red and edematous, with considerable exudate on both tonsils, and a severe bilateral cervical adenitis was present. Type 19 streptococci were isolated on culture of materials from the nose and throat. He was given penicillin as described and then 25 Gm. of sulfadiazine in five days. The concentration of free sulfadiazine in the blood was 9.6 mg. per hundred cubic centimeters on one occasion and 5.3 mg. at another time. On the second day of treatment the patient appeared much better, though he complained of nasal congestion and felt as if he had a "severe head cold." He continued to improve. On the third day of treatment he had an earache, which promptly subsided with the continuation of therapy. After therapy with sulfadiazine was stopped, cultures of material from the throat, which had been negative for streptococci during therapy, promptly became positive for the same type of streptococci. Although he appeared to be completely recovered, a severe·form of acute rheumatic fever subsequently developed. Chart 10 illustrates the clinical course of this patient.

Comment: A patient acutely ill with tonsillitis appeared to make a satisfactory response to penicillin and sulfadiazine. During therapy, cultures of material from the throat remained negative, but they became positive at the conclusion of therapy. Acute rheumatic fever subsequently developed as a sequel to his infection.

CASE 2.—A 19 year old white youth entered the station hospital on March 16, 1944. On the day of entry, headache, fever, sore throat and nonproductive cough developed. The patient appeared extremely toxic. His appetite was poor. The tonsils were noticeably enlarged and reddened, and a moderate amount of exudate covered the surfaces. He had moderate bilateral cervical adenitis. Type 46 streptococci were obtained from the nose and throat on culture. The patient was given 200,000 units of penicillin in amounts of 50,000 units every six hours for four doses. At the same time the last dose of penicillin was administered, sulfadiazine was started, and he received 27 Gm. in five days. The blood level of free sulfadiazine was 7.6 mg. per hundred cubic centimeters. On the second day of therapy, the patient was much improved. The exudate on the tonsils was much less, and the adenitis had diminished in severity. On the fourth day the pharynx appeared normal, there was no adenitis and the patient did not have a sore throat. Eleven days after the beginning of therapy and five days after therapy with sulfa-

diazine had been discontinued, fever and a sore throat developed.   Exudate on the tonsils and adenitis reappeared.   This relapse subsided without specific therapy. All but 1 culture of material from the throat was negative for hemolytic strep-
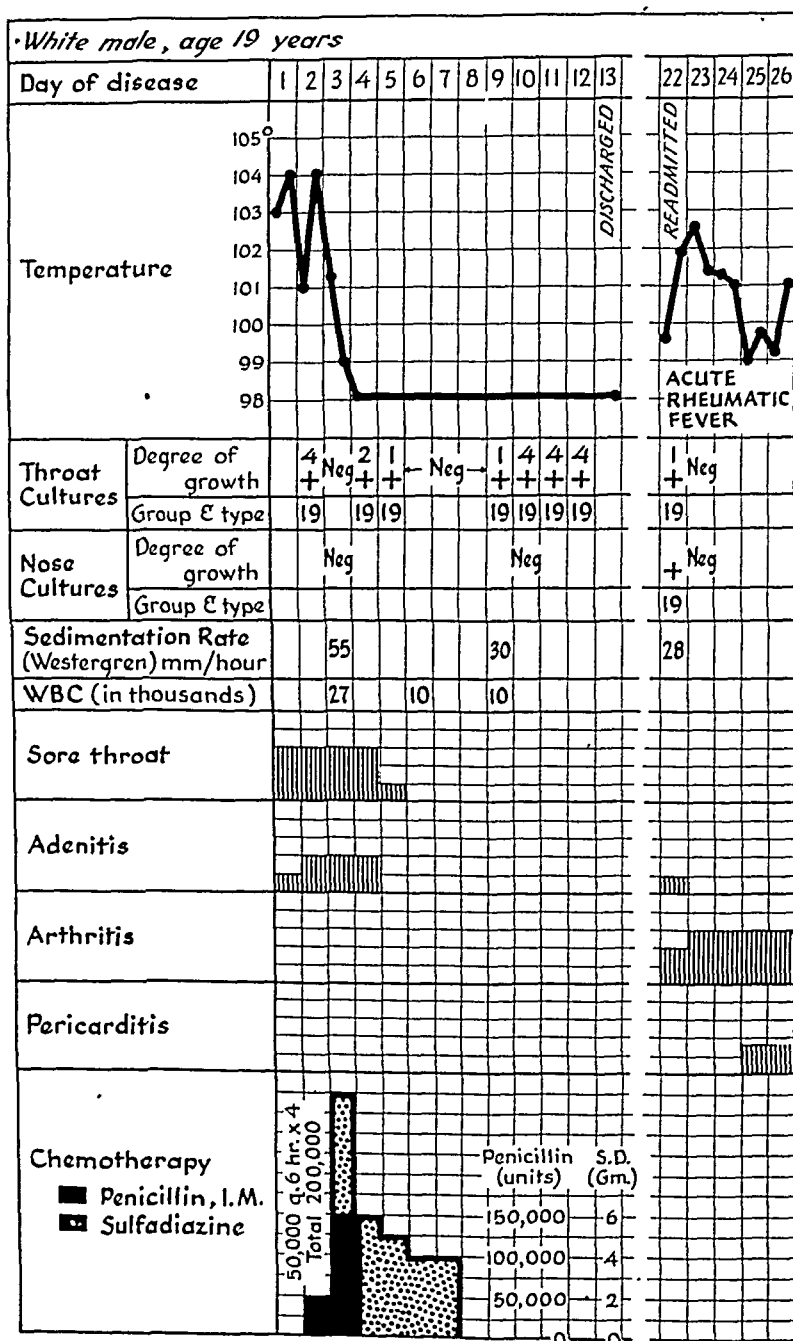
Chart 10.—Effect of 200,000 units of penicillin followed by 25 Gm. of sulfadiazine on the clinical course of severe tonsillitis.   Note the bacteriologic relapse and subsequent development of acute rheumatic fever.

tococci during the period when the patient was receiving penicillin and sulfadiazine. There was an immediate bacteriologic relapse, with the same type of streptococci at the cessation of treatment.   Chart 11 shows the course of this patient.

Comment: A patient with tonsillitis responded satisfactorily to penicillin and sulfadiazine. Following the cessation of therapy, there was a bacteriologic relapse, which, in turn, was succeeded by a clinical relapse. Spontaneous recovery ensued.
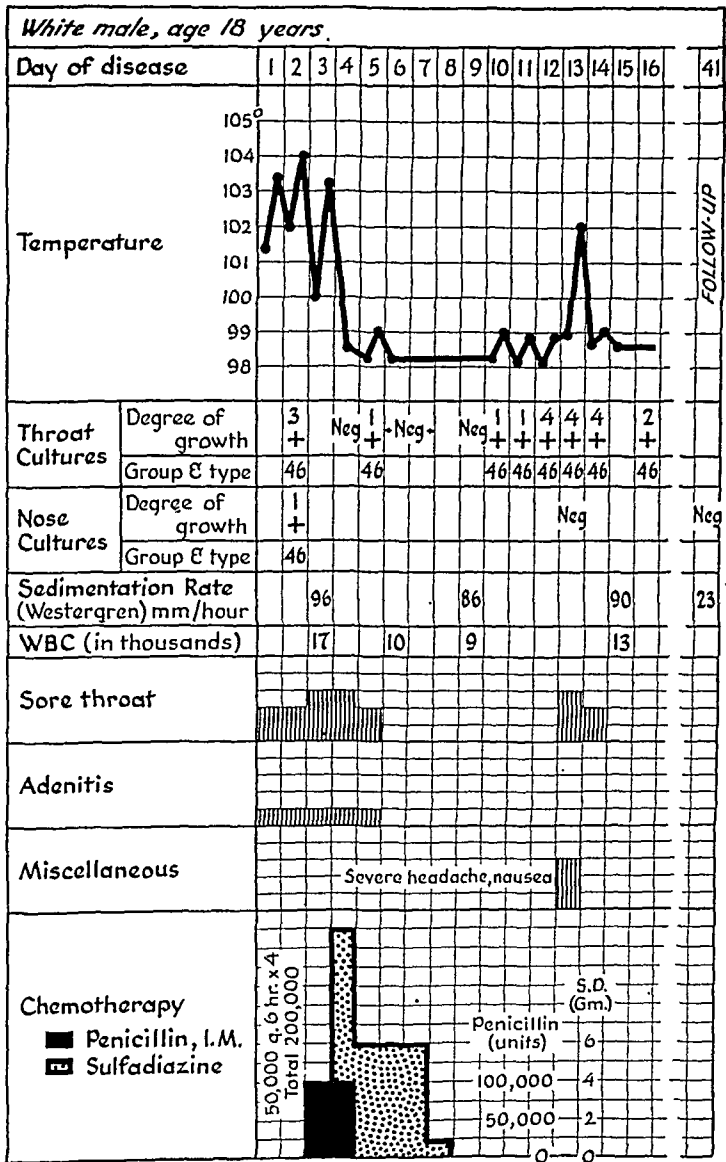
Chart 11.—Effect of 200,000 units of penicillin followed by 27 Gm. of sulfadiazine on the clinical course of severe tonsillitis. Note the clinical and bacteriologic relapse.

In summary, essentially the same clinical response was obtained in patients with tonsillitis when a relatively small total dose of penicillin was followed by therapy with sulfadiazine as was previously described for penicillin. It is significant that a majority of the patients had negative cultures of material from the nose and throat while therapy

was being given. This was primarily due to the penicillin and not to the sulfadiazine. Shortly after therapy with sulfadiazine had been discontinued, the majority of patients had bacteriologic relapses, and in some instances there was a clinical relapse. The mechanism of these relapses has been previously discussed and is possibly related to therapy with penicillin. On the basis of these observations, it would appear that there is no advantage in the use of sulfadiazine in conjunction with penicillin except for patients with unusually severe tonsillitis and patients with complications.

Treatment of Scarlet Fever with Penicillin or Penicillin and Sulfadiazine.—An attempt was made to evaluate penicillin or penicillin and sulfadiazine for patients with scarlet fever. During the period of this investigation the number of cases encountered was relatively small, and, since only the more severely ill patients were selected for the treatment, only 15 were studied. The doses of penicillin and sulfadiazine which were administered and other clinical and bacteriologic data are given in table 8.

Only 2 patients received penicillin alone. One patient received 300,000 units, and a second was given 1,000,000 units. Fairly satisfactory clinical results were obtained in both instances. While the improvement was not dramatic, definite benefit was noted within the first twenty-four hours of therapy. The following case demonstrates the effect of relatively small doses of penicillin on scarlet fever:

CASE 1.—An 18 year old white youth entered the station hospital on Feb. 14, 1944. The day before entry he had a sudden onset of sore throat and fever. On the third day in the hospital, or the fourth day of his illness, he appeared extremely toxic. He had a mild erythematous eruption on his trunk. There was a hemorrhagic rash on the soft palate. The tonsils and pharynx were extremely inflamed, with exudate covering the tonsillar surfaces. A severe bilateral cervical adenitis was present. Type 30 streptococci were obtained from cultures of material from the nose and throat. On the third day of his illness the patient was given 25,000 units of penicillin intramuscularly every four hours for twelve doses, or a total of 300,000 units. On the second day of treatment he felt much better. The rash was less, the redness of the pharynx had diminished, only a slight amount of exudate was present on the tonsils and the adenitis had almost subsided. He continued to improve steadily. The rash was completely absent forty-eight hours after therapy. He made an uneventful recovery. Hemolytic streptococci were not eradicated from the throat. The clinical course of this patient is illustrated in chart 12.

The remaining 13 patients were given penicillin in total doses varying between 200,000 and 400,000 units followed by therapy with sulfadiazine. In general, fairly satisfactory clinical results were obtained. Chart 13 shows a composite chart with the effect of combined therapy on the temperatures of 9 patients with scarlet fever. All the patients improved coincident with therapy. The effect with

TABLE 8.—*Effect of Penicillin Administered Intramuscularly or Penicillin and Sulfadiazine on the Clinical Course and Bacteriologic Status of Patients Having Scarlet Fever*

Total Dose of Penicillin in Units, and Method of Administration	Total Dose Sulfadiazine	Interval Between Initial Treatment and Normal Temperature	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture				Comments
			Before Treatment		After Treatment		
			Nose	Throat	Nose	Throat	
300,000—25,000 every 4 hr. × 12...	....	96 hr.	Type 30, 1+	Type 30, 4+	Type 30, 4+	Type 30, 4+	Fair response
1,000,000—50,000 every 4 hr. × 20...	....	48 hr.	Type 3, 4+	Type 3, 2+	Negative	Type 19, 1+	Fair response; reinfection without symptoms
200,000—50,000 every 4 hr. × 4.....	18 Gm. 4 days	96 hr.	Type 30, 2+	Type 30, 3+	Type 30, 4+	Type 30, 4+	Fair response
200,000—50,000 every 4 hr. × 4......	28 Gm. 5 days	5 days	Negative	Type 19, 3+	Negative	Type 19, 3+	Fair response; on day following conclusion of therapy temperature 100 F. and lasting 6 days
200,000—50,000 every 4 hr. × 4.....	37 Gm. 6 days	72 hr.	Type 19, 4+	Type 19, 4+	Type 19, 1+	Type 19, 2+	Questionable effect
200,000—50,000 every 4 hr. × 4......	26 Gm. 5 days	5 days	Negative	Type 30, 1+	Negative	Negative	Fair response
200,000—50,000 every 4 hr. × 4......	24 Gm. 4 days	96 hr.	Type 17, 2+	Type 17, 1+	Group C, 2+	Group C, 3+	Fair response; 3 days after conclusion of therapy temperature 99 F., with tonsillitis and adenitis on 6th day
200,000—25,000 every 4 hr. × 8.....	25 Gm. 5 days	72 hr.	Type 17, 1+	Type 17, 4+	Negative	Type 17, 1+	Fair response
200,000—25,000 every 4 hr. × 8.....	30 Gm. 5 days	72 hr.	Type 3, 4+	Type 3, 4+	Negative	Type 1, 1+	Fair response; readmitted 1 week after discharge, 22 days after therapy, with acute rheumatic fever and type 1 organisms in throat
200,000—25,000 every 4 hr. × 8.....	26 Gm. 5 days	48 hr.	Type 17, 4+	Type 17, 1+	Negative	Type 0,* 3+	Reinfection; slight febrile relapse on 4th and 5th days after therapy
200,000—50,000 every 6 hr. × 4.....	33 Gm. 6 days	96 hr.	Type 19, 4+	Type 19, 4+	Type 19, 1+	Type 19, 3+	Fair response; 5 days after therapy temperature 99 F., with aches and pains lasting 8 days
200,000—50,000 every 6 hr. × 4.....	33 Gm. 6 days	96 hr.	Type 19, 4+	Type 19, 3+	Type 19, 4+	Type 19, 4+	Readmitted 19 days after treatment, with acute rheumatic fever; type 19 organisms still in nose and throat
200,000—50,000 every 6 hr. × 4......	27 Gm. 5 days	6 days	Type 19, 2+	Type 19, 4+	Type 19, 2+	Type 19, 3+	Fair response; 6th day after treatment slight fever and sore throat
350,000—50,000 every 4 hr. × 7......	50 Gm. 5 days	5 days	Type 3, 4+	Type 3, 3+	Negative	Type 3, 1+	Fair response; mastoiditis aborted
400,000—25,000 every 4 hr. × 16......	14 Gm. 3 days	96 hr.	Type 17, 4+	....	Negative	Type 17, 3+	Fair response; urticaria due to penicillin or sulfadiazine

* Type 0 = unable to type.

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penicillin appeared to be more promising than that experienced with sulfadiazine but not so beneficial as that obtained with the use of specific antitoxin. Though antitoxin was not evaluated in this investigation, previous experience had demonstrated prompt improvement in patients with severe scarlet fever who had received antitoxin. Poststreptococcic fever was observed in several patients after the cessation of therapy, and clinical relapses with sore throat and fever were
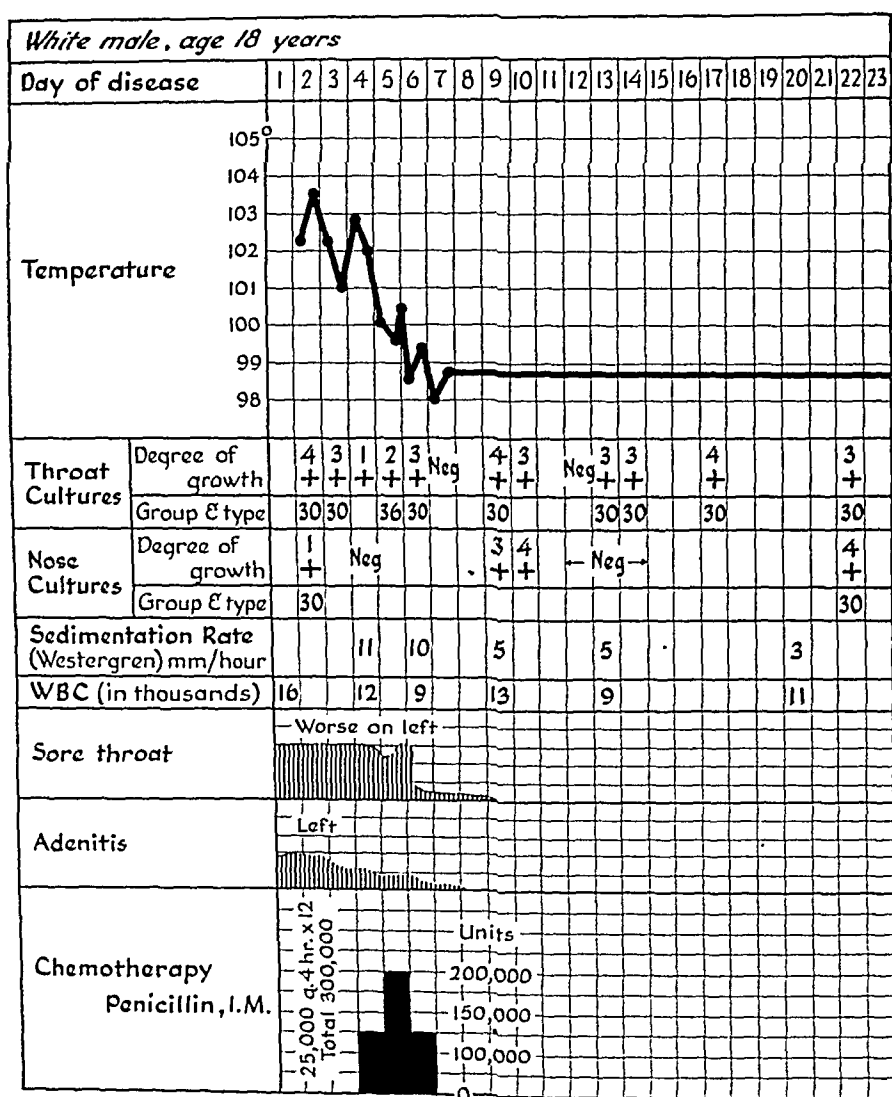
Chart 12.—Effect of 300,000 units of penicillin on the clinical course of scarlet fever. Note that hemolytic streptococci reappeared in the nose and throat before discharge from the hospital.

associated with the reappearance of streptococci in cultures of material from the throat. Acute rheumatic fever developed in 2 patients (patients 9 and 12). One patient had urticaria due to either the penicillin or the sulfadiazine. Chart 14 presents composite data for patients with scarlet fever and the response to different types of therapy.

The failure to obtain a prompt response with penicillin and sulfadiazine in a patient with scarlet fever is demonstrated by the following case.

A 32 year old white man entered the station hospital on March 18, 1944. The day before entry sore throat, headache and vomiting developed. On entry he appeared decidedly toxic. The day after entry, or on the third day of his illness, he had the typical erythematous eruption of scarlet fever on his trunk and extremities. There were extreme redness and edema of the uvula and pharynx. Though his tonsils were absent, there was exudate on the uvula and in the tonsillar fossae.
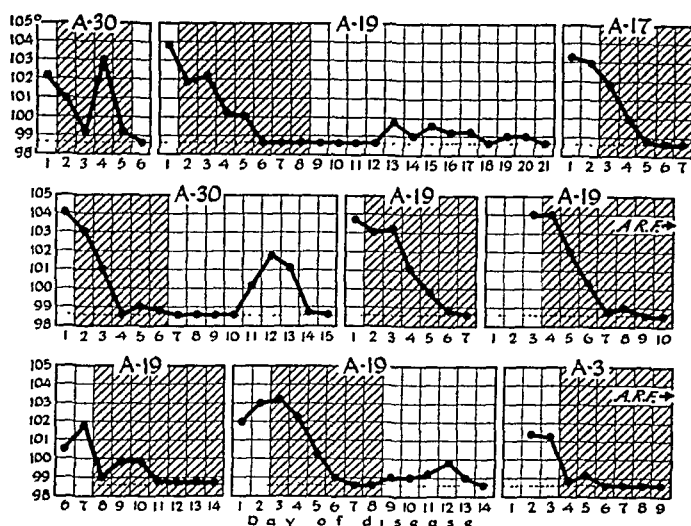
Chart 13.—Composite chart showing effect of 200,000 units and sulfadiazine on the temperatures of 9 patients with scarlet fever. Hatched areas indicate periods when penicillin and sulfadiazine were administered. Note that acute rheumatic fever developed in 2 patients.
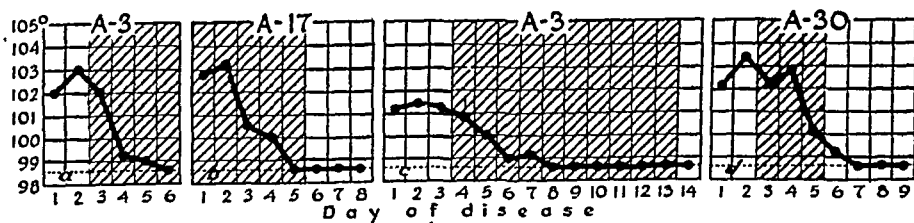
Chart 14.—Effect of miscellaneous forms of treatment on temperatures of patients with scarlet fever: *a*, 1,000,000 units of penicillin; *b*, 400,000 units of penicillin followed by sulfadiazine; *c*, 350,000 units of penicillin, followed by sulfadiazine, and *d*, 300,000 units of penicillin.

Slight bilateral cervical adenitis was present. Type 19 streptococci were isolated from the nose and throat on culture. He was given a total of 200,000 units of penicillin in four doses of 50,000 units every six hours. With the last dose of penicillin, sulfadiazine was administered for a total dose of 33 Gm. in six days. A concentration of 6.5 mg. of free sulfadiazine in the blood was obtained. On the second day of therapy he was improved, though still ill and unable to eat. There was less edema of the pharynx. On the third day he was improved and eating a little. The rash was subsiding, and only a slight amount of exudate was

present on the uvula. On the fourth day the pharynx appeared normal and his appetite was fair. On the fifth day he still had a slight sore throat but the rash had disappeared. There was desquamation of the skin on the seventh day. After therapy the same type of streptococci were cultured from his throat. He also had late poststreptococcic fever. The clinical course of this patient is illustrated in chart 15.
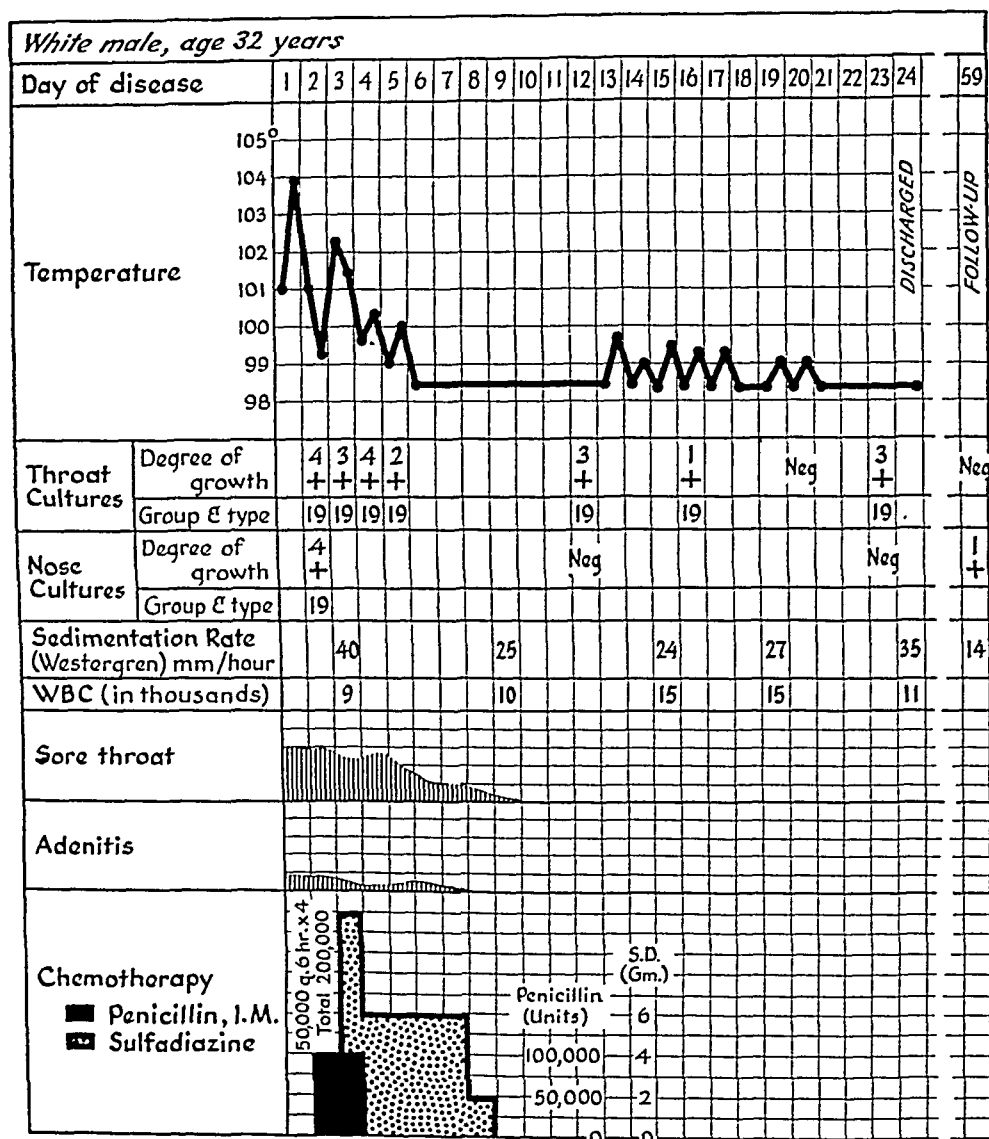
Chart 15.—Effect of 200,000 units of penicillin followed by 33 Gm. of sulfa-diazine on scarlet fever. Note the failure to eradicate hemolytic streptococci from the pharynx and also the poststreptococcic fever.

In summary, it would appear that penicillin and, particularly, penicillin and sulfadiazine are limited in their value against scarlet fever. Specific antitoxin should be given to patients having severe scarlet fever. Penicillin, and possibly sulfadiazine, should be reserved for the suppurative lesions which follow invasion of the tissues by the bacterial cell. This includes instances of severe tonsillitis or pharyngitis with cervical

adenitis, early peritonsillar abscesses and otitis media.   In many cases scarlet fever is a relatively mild infection and specific therapy is not necessary.

COMMENT

It must be emphasized that the investigations being reported on were concerned with young men who were in good health prior to the sudden onset of a hemolytic streptococcus infection of the upper respiratory tract or scarlet fever. The majority of the patients treated would probably have recovered without serious complications if specific therapy had not been used.   In this age group, streptococcic tonsillitis and pharyngitis run relatively benign courses. Suppurative complications are uncommon.   Acute rheumatic fever is apparently not prevented by the administration of sulfadiazine or penicillin once an infection has been established by the invasion of tissues by hemolytic streptococci.   Although the number of patients treated was small, sulfadiazine did not appear to shorten the clinical course of either tonsillitis or pharyngitis.   In the more severely ill patients there was some evidence that sulfadiazine did diminish the severity of the disease so that they were more comfortable at an earlier period than the untreated controls.   The clinical effect with penicillin was more pronounced than that obtained with sulfadiazine.   The severity of the symptoms was reduced more promptly, and, in some instances at least, the clinical course was shortened.   There are two disadvantages in use of penicillin for the treatment of streptococcic tonsillitis and pharyngitis.   First, the material must be injected into the patients at frequent intervals.   This is a decided inconvenience in most circumstances when these infections are being dealt with.   Second, patients not infrequently may have bacteriologic and clinical relapses shortly after therapy with penicillin has been discontinued.   The pathogenesis of these clinical relapses merits further discussion.   The concept was entertained that penicillin, as a potent antistreptococcic agent, inhibited growth of the micro-organisms to such a degree that the bacterial cells were absent on the surface of the mucous membranes of the throat but that they persisted deeper in the tissues.   When therapy with penicillin was discontinued, the remaining organisms began to multiply and found their way to the surface again.   There existed the possibility that by a reduction of the numbers of streptococci with penicillin, but not an entire elimination of them, the immunologic mechanism was disturbed in an unfavorable manner for the host.   The natural course of tonsillitis and pharyngitis, and particularly recovery from the diseases, may depend on the presence of streptococci in the throat in sufficient numbers to serve as antigenic material, thus producing local tissue immunity or, possibly, a general immune response. Reducing the numbers of streptococci or altering their metabolic activity with

penicillin might possibly interfere with a desired immune mechanism. With the failure of the host to develop this immunity or because of a partial immunity, the multiplying bacterial cells at the conclusion of therapy with penicillin cause a recurrence of the disease and, in addition, complications. Sulfadiazine, on the other hand, does not interfere with bacterial activity to such an extent that the drug interferes with the immune mechanism. Therefore, relapses do not occur so frequently following the use of sulfadiazine. Obviously, the ideal therapy would be to eliminate streptococci completely from the tissues early in the course of the disease, but the doses of penicillin did not produce this desired result.

Therapy with sulfadiazine did not appear to eradicate streptococci from the pharynx of patients with tonsillitis, pharyngitis and scarlet fever to any greater degree than that manifested in untreated control patients. On the other hand, when as little as 200,000 units of penicillin was given in divided doses, hemolytic streptococci were often absent from the nose and throat during the period of therapy. More than temporary eradication of streptococci from the pharynx was accomplished only with total doses of 500,000 to 1,000,000 units. It appeared that the time over which penicillin is given is as important as the total dose used in the attempt to eradicate streptococci from the throat. This fact is significant in any efforts that are made to eliminate the carrier state of hemolytic streptococci.

Since sulfadiazine did not appear to shorten the clinical course of patients with tonsillitis or pharyngitis and did not eliminate streptococci from their throats, use of sulfadiazine in these infections is definitely indicated only for persons with severe forms of these diseases and for those with suppurative complications. In general, this also applies to penicillin. Total doses of 200,000 units of penicillin may be anticipated to produce some relief for the patients, but doses of 500,000 to 1,000,000 units are necessary if it is desired to eliminate streptococci from the pharynx. There does not appear to be any advantage, at least for the majority of patients, in following up penicillin with sulfadiazine.

Specific antitoxin or serum from patients convalescing from scarlet fever is to be preferred to sulfadiazine and penicillin in the treatment of patients with severe scarlet fever. Sulfadiazine, and especially penicillin, are indicated for the local inflammatory reaction in the throat and suppurative complications.

It is significant that sulfadiazine or penicillin in the doses used did not prevent the development of acute rheumatic fever in patients with infections of the upper respiratory tract due to group A hemolytic streptococci.

SUMMARY

1. An investigation of the therapeutic effectiveness of sulfadiazine and penicillin for acute infections of the upper respiratory tract due to hemolytic streptococci, including scarlet fever, involved observations carried out in a total of 210 young men in one area during a period of four months.

2. Cultures of materials from the nose and throat were made, and when hemolytic streptococci were isolated grouping and typing of the organisms were performed according to the method of Lancefield. Approximately 2,000 cultures were studied during the course of this investigation.

3. One hundred and two patients having acute tonsillitis or nasopharyngitis were used as a control series and did not receive sulfadiazine or penicillin. Seventeen patients with tonsillitis or nasopharyngitis were given sulfadiazine. Thirty patients with moderate to severe forms of tonsillitis and 9 patients having severe nasopharyngitis received penicillin. Penicillin was also given to 8 patients with nonstreptococcic infections of the upper respiratory tract, 2 patients with scarlet fever and 1 with erysipelas. Penicillin followed by sulfadiazine was administered to 13 patients with scarlet fever and to 16 patients with tonsillitis.

4. Sulfadiazine did not shorten the clinical course of patients with tonsillitis or eradicate hemolytic streptococci from the pharynx. In severely ill patients the drug did appear to diminish the severity of the disease more rapidly than the natural diminution which occurred in the untreated controls.

5. Total doses of 200,000 units of penicillin given intramuscularly to patients with severe tonsillitis and nasopharyngitis reduced the severity and in some instances appeared to shorten the duration of the disease. Doses of 500,000 to 1,000,000 units were necessary before hemolytic streptococci were eliminated from cultures of material from the throat for more than a temporary period.

6. Clinical relapses following the administration of penicillin were frequently encountered and appeared to be related to the reappearance of hemolytic streptococci in the throat.

7. Penicillin followed by sulfadiazine did not appear to have any advantages over penicillin alone in the treatment of tonsillitis. This combination did not produce too satisfactory results in patients having scarlet fever.

8. Penicillin did not appear to prevent the subsequent development of acute rheumatic fever in patients having nasopharyngitis, tonsillitis and scarlet fever due to group A hemolytic streptococci.

REITER'S DISEASE

Review of the Literature, with Presentation of a Case

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THE triad of symptoms consisting of urethritis, conjunctivitis and arthritis, common in gonorrhea, has more recently been observed in patients in whom the etiologic role of the gonococcus could not be established. The first case was described by Reiter [1] in Germany in 1916. During the first world war this German physician observed a lieutenant on the eastern front who was suffering from abdominal cramps and bloody diarrhea. Later purulent urethritis and conjunctivitis appeared, followed shortly thereafter by arthritis of the left knee, right elbow, left wrist and joints of the fingers of the right hand, in that order. Subsequently cystitis, edema of the prepuce, iritis, enlarged spleen and pustular lesions over the left hip were noted. Reiter was unable to influence the disease by any of the therapeutic agents available to him. His major contribution ʌis that he conceived of this syndrome as a new entity not ascribable either to dysentery or to gonorrhea. At about the same time two other clinicians made independent reports of this disease, Fiessinger [2] in France and Macfie [3] in Africa. Subsequently a large number of similar publications appeared in the French, German and Scandinavian literature. [4]

1. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetoṣis arthritica), Deutsche med. Wchnschr. **42**:1535, 1916.

2. Fiessinger, N., and Leroy, E.: Contribution à l'étude d'une épidémie de dysenterie dans la Somme (Juillet-Octobre, 1916), Bull. et mém. Soc. méd. d. hôp. de Paris **40**:2030, 1916-1917.

3. Macfie, J. W. S.: Urethral Spirochaetosis, Parasitology **9**:274, 1917.

4. (*a*) Balban, W.: Zur Kenntnis der sog. "Spirochaetosis arthritica" (Reiter), Dermat. Ztschr. **68**:305, 1934. (*b*) Beck, F.: Ein Beitrag zu der sog. Spirochaetosis arthritica Reiter, Med. Klin. **33**:1162, 1937. (*c*) Besson, A., and Ehringer, G.: Diagnostic des arthrites dysentériques, Paris méd. **2**:328, 1926. (*d*) Gounelle, H.; Bohn, A.; Koskas, C., and Marche, J.: Sur la maladie rhumatismale post-dysentérique (formes fébriles prolongées, syndrome sanguin et humoral, altérations osseuses, essais thérapeutiques), Bull. et mém. Soc. méd. d. hôp. de Paris **56**:821, 1941. (*e*) Clemmesen, S., and Kalbeck, K.: Polyarthritis Urethrica Simplex in Four Patients, Ugesk. f. læger **100**:618, 1938. (*f*) Dorendorf: Der Ruhrrheumatism, Med. Klin. **13**:519, 1917. (*g*) Fleischmann, in discussion on Reiter. [1] (*h*)

The first American description appeared twenty-five years after the syndrome had been recognized in Europe. A report by Bauer and Engleman [5] describing the classic features of the disease in a young college student is apparently the first instance observed and recorded in the United States. It is also the only full report in the American literature, other contributions [6] being limited to special aspects of the disease.

Foerster, R.: Zwei Fälle von Reiterscher Erkrankung, Med. Welt **7**:700, 1933. (*i*) Freund, E.: Die Gelenkserkrankungen, Berlin, Urban & Schwarzenberg, 1928, p. 142. (*j*) Frühwald, R.: Beitrag zur sogenannten Spirochaetoses arthritica (Reiter), Dermat. Ztschr. **51**:35, 1927-1928. (*k*) Germain, A., and Pirot, R.: Syndrome conjonctivo-uréthro-synovial, complication métastatique d'un état dysentériforme, Arch. de méd. et pharm. nav. **125**:302, 1935. (*l*) Hombourger, P.: Syndromes oculo-articulaire d'origine dysentérique, Soc. de méd. mil. franç., Bull. mens. **22**:33, 1928; (*m*) Contribution à l'étude des complications oculaires, et articulaires de la dysentérie bacillaire (syndrome conjunctivo, uretro, synovial de Noël Fiessinger), Rev. gén. de clin. et de thérap. **44**:459, 1930. (*n*) Junghanns, O.: Ein weiterer Fall von Urethritis nongonorrhoica und septischer Allgemeinerkrankung, Deutsche med. Wchnschr. **44**:1304, 1918. (*o*) Kielland, J.: Polyarthritis Dysenterica, Nord. med. **2**:984, 1939. (*p*) Kristensen, M.: Case Report on a Case of Reiter's Disease, Acta path. et microbiol. Scandinav. **7**:87, 1930. (*q*) Kristjansen, A.: Nongonorrheal Urethritis with Conjunctivitis and Arthritis, Ugesk. f. læger **??**:276, 1930. (*r*) Kruspe, H.: Zur Aetiologie der Reiterschen Erkrankung, Dermat. Wchnschr. **112**:457, 1941. (*s*) Kuske, H.: Ueber die Hauterscheinungen bei Morbus Reiter, Arch. f. Dermat. u. Syph. **179**:58, 1939. (*t*) Maresch and Chiari, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 6, p. 246. (*u*) Michael, M.: Beiträge zur Kasuistik und Differential-Diagnose seltener frühluetischer und gonorrhoischer Komplikationen, Dermat. Ztschr. **24**:406, 1917. (*v*) Musger, A.: Bakteriologische Untersuchungen an einen Fall mit Reiterschen Krankheit, Dermat. Ztschr. **68**:310, 1934. (*w*) Naegeli, cited by Kruspe.[4r] (*x*) Paetzel, H.: Ueber Polyarthritis nach unspezifischer Urethritis, Med. Klin. **24**:134, 1928. (*y*) Pfleger, R.: Zur Aetiologie der Reiterschen Erkrankung, ibid. **33**:465, 1937. (*z*) Postma, C.: A Case of Reiter's Disease, Acta dermat.-venereol. **18**:691, 1937. (*a'*) Reiter, H.: Ueber die Spirochaete forans, Zentralbl. f. Bakt. (Abt. 1) **79**:176, 1916-1917; (*b'*) Ueber die sogenannte "Spirochätosis arthritica" (Reiter), München. med. Wchnschr. **68**:950, 1921. (*c'*) Rist, S.: Arthropathies et conjonctivites dysentériques, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1762, 1916. (*d'*) Ruge, H.: Bemerkungen zu der Arbeit von Frühwald: "Spirochaetosis arthritica," Dermat. Ztschr. **54**:98, 1928. (*e'*) Salvesen, H. A.: Dysenteric Polyarthritis and Enteric Polyarthritis, Norsk mag. f. lægevidensk. **98**:953, 1937. (*f'*) Schittenhelm, A., and Schlecht, A.: Polyarthritis enterica, Deutsches Arch. f. klin. Med. **26**:329, 1918. (*g'*) Schittenhelm, A., in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 3, Berlin, Julius Springer, 1934, vol. 1, p. 177. (*h'*) Scheuermann, H., cited by Kruspe.[4r] (*i'*) Sommer, A.: Drei wahrscheinlich als "Spirochaetosis arthritica" (Reiter) anzusprechende Krankheitsfälle, Deutsche med. Wchnschr. **44**:403, 1918. (*j'*) Stuehmer, A.: Ueber die sogenannte "Spirochaetosis arthritica" (Reiter), München. med. Wchnschr. **68**:769, 1921; (*k'*) Therapeutische Umfrage: Behandlungsaussichten der nichtspezifischen Urethritiden (Pseudogonor-

The following case was recently observed at the Mount Sinai Hospital, New York.

REPORT OF CASE

History.—A 33 year old Jewish man entered the Mount Sinai Hospital on May 21, 1932 complaining of attacks of urethritis, conjunctivitis and arthritis accompanied by fever, which had recurred over an eight year period. The first attack was ushered in with a thick, mucoid discharge from the urethra. A number of days later fever developed associated with a migratory polyarthritis involving many joints, specifically the left knee, right ankle, spine and the shoulders. The affected joints were red, swollen and extremely tender for approximately one week. Concurrent with the arthritis an acute conjunctivitis developed with purulent discharge, which lasted for several weeks. He had had two such attacks, eight years and two years before admission. Both episodes lasted a few weeks, and all symptoms and findings disappeared completely. Aside from these episodes, two years before admission iritis of the left eye developed which responded to ordinary therapy. He entered the hospital in May 1932 because of recurrence of these symptoms.

Throughout the eight year period, during and following the attacks, many smears for gonococci, blood cultures and gonococcus complement fixation tests were negative.

Examination.—Physical examination revealed an undernourished man appearing chronically ill. The pupils were unequal and irregular, the left showing posterior synechiae, evidence of an old iritis. There was moderate conjunctivits of both eyes. The liver was palpable 1.5 cm. below the costal margin. The left wrist, left index and ring fingers, right ankle and left knee were tender, and their motion was slightly impaired. The thoracic vertebrae were markedly tender, .

rhoen), Dermat. Wchnschr. **93**:1553, 1931. (*l'*) Thesleff, C.: Case of Non-Gonorrheal Urethritis with Articular and Ocular Complications, Finska läk.-sällsk. händl. **80**:411, 1937. (*m'*) Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1920, vol. 4, p. 394. (*n'*) Tiemann: Ueber die Poly-arthritis rheumatica enterica, Ztschr. f. klin. Med. **122**:724, 1932. (*o'*) Wiedemann, H.: Reitersche Erkrankung, Wien. klin. Wchnschr. **47**:1245, 1934. (*p'*) Worms, G.; Lesbre, P., and Sourdille, G.: Specificité des infections oculo-articulaires tardives dans les dysentéries bacillaires, Compt. rend. Soc. de biol. **95**:1042, 1926. (*q'*) Worms, G., and Sourdille, G.: Complications oculaires des entéropathies à germes spécifiques, Arch. d'opht. **45**:737, 1928. (*r'*) Worms, G.; Sourdille, G., and Lesbre, P.: Syndrome oculo-articulaire au décours d'une épidémie de dysentérie à bacilles de Hiss, Bull. Soc. d'opht. de Paris, 1927, pp. 21-28. (*s'*) Worms, G.; Lesbre, P., and Sourdille, G.: Syndrome oculo-articulaire au décours d'une épidémie de dysénterie à bacilles de Hiss, Soc. de méd. mil. franç., Bull. mens. **21-22**:29, 1927-1928.

5. Bauer, W., and Engleman, E. P.: A Syndrome of Unknown Etiology Characterized by Urethritis, Conjunctivitis and Arthritis (So-Called Reiter's Disease), Tr. A. Am. Physicians **57**:307, 1942.

6. (*a*) Colby, F. H.: Renal Complications of Reiter's Disease, J. Urol. **52**:415, 1944. (*b*) Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. **49**:389 (June) 1944. (*c*) Rosenblum, H. H.: So-Called Reiter's Disease: The Triad of Acute Arthritis, Conjunctivitis and Urethritis, U. S. Nav. M. Bull. **44**:375, 1945.

particularly the third and seventh. The urethral meatus was reddened. The prostate was normal; the skin was clear. Neurologic examination revealed no abnormalities.

Laboratory data.—Blood culture was negative and prostatic fluid obtained by massage contained no gonococci. Reactions to the Wassermann and gonococcus complement fixation tests were repeatedly negative. The urine was normal. Fluid aspirated from the left knee joint was cultured one week before admission and was reported negative. The electrocardiogram was normal. Roentgen examination of the left knee showed irregular areas of rarefaction of the condyles, a finding which was interpreted as a destructive process.

Course.—During his two months in the hospital the temperature ranged between 99 and 101 F., finally falling to normal. Under observation bilateral herpetic corneal ulcers developed, which responded to administration of atropine and use of hot compresses. To eliminate possible foci of infection, tonsillectomy was performed. This was followed by transient arthralgias.

The patient was finally discharged to his private physician with recommendations for physical therapy.

Second Admission.—On Feb. 11, 1935, the patient was again admitted to the hospital. He had remained well and asymptomatic. He had carried on his occupation and participated in vigorous sports without disability until seven weeks before admission, when general malaise and vague aches and pains in the back and arms gradually developed. This was soon followed by a heavy urethral discharge lasting two weeks. Urethral smears again failed to reveal gonococci. A week after the onset of the discharge in rapid succession there developed pain, swelling and tenderness of both hip joints, right knee, both ankles, right elbow and left wrist, lasting about one week. At the same time a painful bilateral conjunctivitis appeared, worse in the right than in the left eye. He had a low grade fever, with a temperature up to 100 F. During the early part of the illness he suffered from severe anorexia and nausea; he vomited frequently, slept poorly and lost 20 to 30 pounds (9 to 13 Kg.) during this period. A week after the onset of the illness, a herpetiform lesion appeared on the glans penis, which ruptured and gradually healed. The scar was present on admission. There were no other cutaneous manifestations.

On physical examination the right eye showed circumcorneal injection and numerous superficial infiltrations at 5 and 7 o'clock near the limbus. No deposits were seen on the posterior surface of the cornea. This was considered to be a mild, superficial herpetic keratitis. The left eye showed multiple posterior synechiae. There were several erythematous, glazed areas with brownish crusts on the glans penis. The urethral meatus was normal and contained no discharge even after prostatic massage. Rectal examination gave normal results. The right elbow was slightly tender and warm, with moderate periarticular swelling and definite limitation of extension. The left wrist was tender, stiff and somewhat swollen, with marked swelling of the third left metacarpophalangeal joint. There was a small effusion in both knee joints, and both ankles were tender.

Laboratory Data: Hemoglobin was 70 per cent (Sahli). The white cell count was 14,400 with a normal differential count. The erythrocyte sedimentation time was ten minutes (Linzenmeier). The urine was normal. The Wassermann and gonococcus complement fixation reactions were again negative. Blood culture was negative. Cultures of the prostatic secretions were negative for the gonococcus.

Course: The temperature ranged between 99.5 and 100.6 F. for the first two weeks. Iritis and keratitis soon developed in the left eye, but gradually cleared. A tonsillar stump was surgically removed. Following operation there was a flare-

up of fever, conjunctivitis, iritis and arthritis but not of the urethritis. The symptoms and signs gradually subsided with symptomatic therapy.

Third Admission.—The patient was admitted on June 25, 1941 for a recurrence of severe polyarthritis and urethritis and herpes of the penis. During this episode there were no ocular manifestations or fever. The patient had lost 30 pounds in the three months prior to admission.

Physical examinations on this admission gave essentially the same results as on preceding occasions except for the following additions: The right pupil was fixed to light; there was a lenticular cataract limiting vision to light perception. The liver was palpable 2 cm. below the costal margin. There was a flexion contracture of the right elbow. The left ankle was slightly swollen and there was tenderness over the tenth and eleventh thoracic vertebrae and the first metacarpophalangeal joints.

Laboratory examination revealed the following significant findings: Culture of the urine showed enterococci. The erythrocyte sedimentation time was fifteen minutes. The hemoglobin was .65 per cent. The electrocardiogram, which had previously been normal, now revealed a P-R interval of 0.26 second and slight elevation of the R-T segments in leads II and III. Roentgen examination of the left hip showed no abnormality, but in the dorsal part of the spine there were calcified deposits in the lateral spinous ligaments. The patient was given 400 r of roentgen radiation to the dorsal part of the spine. He was discharged somewhat improved.

Fourth Admission.—The patient was again admitted on March 17, 1943. Five days before admission a watery, urethral discharge developed associated with mild dysuria and followed four days later by a moderate polyarthritis. The right eye was atrophic. There was an iris bombé in the right eye and a streak of exudate at the pupillary margin of the left eye. The pharynx was injected. The lungs were clear. The blood pressure was 110 systolic and 70 diastolic. There was no glandular adenopathy. The abdomen was normal. The urethral meatus was reddened, the prostate large and boggy. The dorsal spine was painful and tender. Redness and heat were present over the dorsum of the right foot and over the upper third of the left fibula.

On laboratory examination the blood count and urinalysis gave normal results. The urethral smear did not contain gonococci, nor were they found in cultures of the prostatic secretions. All serologic reactions, including a brucella agglutination, were negative as before. Blood urea nitrogen was 10 mg. per hundred cubic centimeters, sugar 85 mg., total protein 7 Gm., albumin 4.6 Gm., globulin 2.4 Gm. and uric acid 4.6 mg. Fluid from the knee joint was sterile on culture. The electrocardiogram revealed a P-R interval of 0.2 second and prominent P waves. Roentgen examination of the lungs and hands showed that they were normal. Slight osteoarthritic changes were present in the left knee joint. Calcification was present in the lateral spinous ligaments in the lower thoracic region.

No other foci of infection could be found. The patient was treated with hyperthermia, both by typhoid vaccine and by external heat, but was not benefited. Toward the end of his stay in the hospital he became uncooperative. He refused therapy and was discharged for chronic care.

COMMENT

The earliest sign of this syndrome is frequently diarrhea. If this is absent the disease may begin with either urethritis or conjunctivitis.

The cases published in the French literature were always preceded by diarrhea, and apparently these clinicians were unwilling to diagnose the disease unless it followed an episode of diarrhea. Most of the German writers, on the other hand, recognized that although the majority of these patients do have diarrhea as an initial sign, approximately one third of the cases began with either conjunctivitis or urethritis and never presented an enteric episode.[4x]

When the diarrhea does occur it is usually mild.[7] A low grade fever is commonly present, but by and large the enteric symptomatology is so light that only specific questioning brings out the history. Bloody stools have been noted occasionally.

The enteric phase of the disease usually subsides in less than a week[8] and the patient remains well until ten to thirty days later, when a purulent conjunctivitis and urethritis appear. The conjunctivae become hyperemic and edematous and a yellowish mucopurulent discharge appears.[4q'] Most commonly only conjunctivitis results but occasionally keratitis,[9] iritis and iridocyclitis[10] occur, as they did in the patient whose case I have reported. Urethritis appears at about the same time, preceding or following the conjunctivitis by one or two days. The patient complains of dysuria and frequency.[1] A yellow, mucopurulent discharge exudes freely from the urethra. Not infrequently cystitis,[11] prostatitis[5] and prostatic abscess[6a] have been noted. Colby[6a] describes pyelonephritis as a complication of the syndrome. The urethritis and conjunctivitis persist throughout the entire course of the disease, with occasional remissions and exacerbations.

As the disease progresses, the weight-bearing joints, particularly those of the ankle and knee, become acutely inflamed and tender.[12] Less commonly the hips, shoulder, wrists, finger joints or even the vertebral column are affected.[13] Usually multiple joints are involved, and the arthritis is migratory, resembling the picture of acute rheumatic arthritis. Tendovaginitis has been described.[14] The roentgen examination does not reveal destructive changes, and usually full function remains. However, ankylosis has been reported[15] and was found to

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7. Hombourger.[4m] Schittenhelm and Schlecht.[4f']

8. Reiter.[1] Hombourger (footnote 4*l* and *m*). Schittenhelm and Schlecht.[4f'] Worms, Lesbre and Sourdille.[4p'] Worms and Sourdille.[4q'] Worms, Sourdille and Lesbre.[4r'] Worms, Lesbre and Sourdille.[4s']

9. Beck.[4b] Worms and Sourdille.[4q']

10. Reiter.[1] Freund.[4i] Worms and Sourdille.[4q']

11. Reiter.[1] Sommer.[4i'] Bauer and Engleman.[5] Colby.[6a]

12. Schittenhelm and Schlecht.[4f'] Hombourger.[4m] Kuske.[4s]

13. Reiter.[1] Schittenhelm and Schlecht.[4f'] Hombourger.[4m]

14. Dorendorf.[4f] Schittenhelm and Schlecht.[4f']

15. Paetzel.[4x] Lever and Crawford.[6b]

be present in my case. Hydroarthroses are common and usually resolve spontaneously.[16] Serous fluid with low protein content is obtained on tap. Lymphocytes and polymorphonuclear cells are present in about equal proportion. Culture of the joint fluid is sterile.

During this period the patient has a low grade fever.[17] There is usually no anemia, but a moderate elevation of the polymorphonuclear cell count has been described by almost all observers, as well as an increase in the erythrocyte sedimentation rate.

Physical examination frequently reveals generalized lymphadenopathy especially of the axillary and inguinal nodes.[18] Occasionally a moderate splenomegaly is found.[19] Pleuritis has been mentioned.[4f'] In a minority of cases and late in the disease lesions of the skin appear.[20] These begin as small superficial vesicles, change into shallow ulcers and finally heal, leaving hyperkeratotic scars. This complication has been described independently of Reiter's disease as keratosis blenorrhagica of nongonorrheal etiology.[21] The site of predilection is usually over the affected joints, especially in the lower extremities, and over the scrotum and penis. In the latter areas the lesions of the skin resemble herpes progenitalis in their early stages.

In 2 cases epistaxis was a frequent event [22] and in 1 an abnormally prolonged clotting time and poor clot retraction were found.[4d] In 1 other case bilateral involvement of the pyramidal tract was noted.[18b] Because of the infrequency of these manifestations they must be regarded as incidental.

Incomplete syndromes have occurred. Urethritis and arthritis without either conjunctivitis or cutaneous lesions have been observed.[23]

16. (*a*) Wepler, W.: Zur Morphologie und Pathogenese der post-dysenterischen Polyarthritis, Beitr. z. path. Anat. u. z. allg. Path. **106**:289, 1942. (*b*) Hombourger.[4m] (*c*) Worms, Lesbre and Sourdille.[4p'] (*d*) Schittenhelm and Schlecht.[4f'] (*e*) Bauer and Engleman.[5]

17. Reiter.[1] Hombourger.[4m] Schittenhelm and Schlecht.[4f'] Worms and Sourdille.[4q']

18. (*a*) Moltke, O.: Polyarthritis Urethritica, Acta med. Scandinav. **89**:606, 1936. (*b*) Usseglio, G., and Zancan, B.: Il morbo di Reiter, Arch. per le sc. med. **69**:79, 1940. (*c*) Postma.[4z] (*d*) Bauer and Engleman.[5]

19. Reiter.[1] Usseglio and Zancan.[18b]

20. (*a*) Baermann, G.: Ueber hyperkeratotische Exantheme bei schweren gonorrhoischen Infektionen, Arch. f. Dermat. u. Syph. **69**:363, 1904. (*b*) Beck.[4b] (*c*) Kuske.[4s] (*d*) Postma.[4z] (*e*) Bauer and Engleman.[5] (*f*) Lever and Crawford.[6b]

21. Buschke, A., and Michael, M. J.: Zur Kenntnis der hyperkeratotischvesikulösen Exantheme bei Gonorrhoe, Arch. f. Dermat. u. Syph. **120**:348, 1914. Chajes, B.: Ueber nichtgonorrhoische Urethritiden und ihre Komplikationen, Dermat. Centralbl. **17**:194, 1913-1914.

22. Gounelle, Bohn, Koskas and Marche.[4d] Hombourger.[4m]

23. Kristjansen.[4q] Bauer and Engleman.[5] Moltke.[18a] Baermann.[20a]

Conjunctivitis and diarrhea both with and without arthritis have also been noted.[24]

It is necessary to differentiate Reiter's disease from the gonorrheal syndrome consisting of urethritis, conjunctivitis and arthritis. This differentiation can be made only by thorough bacteriologic investigation. In Reiter's disease bacteriologic studies of blood, urethral and conjunctival secretions and joint fluid never reveal gonococci. The reaction to the gonococcus complement fixation test is always negative.

AGE AND SEX

Reiter's disease probably occurs only in men. Most cases have been in men in their early twenties, the youngest patient whose case was reported being 16[4n] and the oldest 45. Only 1 case in a female has been described,[6b] and this was so atypical in other respects as to cast doubt on its being a case of Reiter's disease.

GEOGRAPHIC DISTRIBUTION

Although most of the observed instances of this disease have been in Germany, France and Scandinavia, it is probable that this distribution merely reflects the earlier interest of European physicians. Similar cases were described by Woodward[25] in his "Medical and Surgical History of the War of the Rebellion." More recently 10 cases have been reported in American soldiers on duty in the Pacific area[6c] and Bauer and Engleman[5] report that they have seen 6 cases in Boston.

It might be assumed from the infrequent mention of this disease in the literature that it is of rare occurrence. However, certain clinicians, notably Fiessinger,[2] Hombourger,[41,m] Worms and Sourdille,[26] and Schittenhelm and Schlecht[4f'] have each observed a considerable number of cases, Hombourger reporting 56. It seems likely therefore that many cases in which the condition is being regarded now as nonspecific

24. (*a*) Graham, G.: Arthritis in Dysentery: Its Causation, Prognosis and Treatment, Proc. Roy. Soc. Med. **13**:23, 1919. (*b*) Graham, D., in Nelson's Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1937, vol. 2, p. 172. (*c*) Maxwell, E. M., and Kiep, W. H.: Notes on Six Cases of Iritis and Cyclitis Occurring in Dysenteric Patients, Brit. J. Ophth.. **2**:71, 1918. (*d*) Pemberton. R.: The Relation of the Gastrointestinal Tract to the Syndrome of Arthritis, Rev. Gastroenterol. **9**:91. 1942. (*e*) Pribram. A.: Der akute Gelenksrheum ̄mus, Vienna, A. Holder, 1899, pp. 397-399. (*f*) Pillat, A.: Augenärztliches zum Rheumatismusproblem, Wien. klin. Wchnschr. **49**:385, 1936. (*g*) Zia, S. H., and Smyly, H. J.: Arthritis in Association with Bacillary Dysentery, Nat. M. J. China **17**:307, 1931. (*h*) Schittenhelm and Schlecht.[4f'] (*i*) Schittenhelm.[4g']

25. Woodward, J. J.: Medical and Surgical History of the War of the Rebellion, Washington, D. C., Government Printing Office, 1879

26. Worms, Lesbre and Sourdille.[4p'] Worms and Sourdille.[4q'] Worms, Sourdille and Lesbre[4r'] Worms, Lesbre and Sourdille.[4s']

conjunctivitis and urethritis or as rheumatoid arthritis may well be examples of Reiter's disease.

PATHOLOGY

In only 2 cases were the pathologic tissues from patients with this disease examined. Bauer and Engleman[5] studied a small piece of synovial tissue removed for biopsy from the left knee joint, and found a suggestion of villous formation in the suprapatellar pouch. On microscopic examination the intima was found to be several cells deep, and contained a moderate excess of lymphocytes and plasma cells and a few leukocytes. There was no evidence of exudate, and no inclusion bodies were found. A scant, diffuse infiltration of inflammatory cells was present throughout the subintimal layers. The pathologic diagnosis was mild synovitis with marked hyperemia.

Almost the same microscopic changes were reported by Wepler,[16a] who observed a case of typical Reiter's disease following an intestinal disorder. The patient apparently died of massive bleeding in the gastrointestinal tract. At postmortem examination a rupture of a submucous vessel in the wall of the stomach was found. There was no ulcer, no thrombus and no inflammatory response. Examination of the knee showed normal cartilage with a greenish yellow fluid in the joint. Microscopically there were edema of the synovia and disappearance of the synovial lining cells. The joint capsule was infiltrated with lymphocytes, as was the periarticular tissue. The joint exudate consisted mainly of polymorphonuclear cells. Cartilage and bone showed no changes from the normal.

FREQUENCY AND PROGNOSIS

A total of 151 cases have been reported in the literature to date. As indicated in the foregoing text, most of them were seen in Germany and France.

The prognosis for life is excellent. In no case has the disease itself caused death. Nevertheless, in isolated instances extensive ocular injuries occur. Also, as exemplified by the case reported, ankylosis and resultant limitation of function do occur.

The natural course of the disease is self limited, usually terminating in two to four months. However, relapses are not unusual and may occur over a period of many years. In Freund's case[41] a relapse occurred ten years after the onset of the illness, and the patient whose case I have reported had recurrences over the course of sixteen years.

ETIOLOGY AND EPIDEMIOLOGY

The cause of this syndrome is obscure. Almost as many etiologic agents have been indicated as there have been authors describing the

syndrome.   High agglutination titers against dysentery organisms
have led certain authors to consider them as causative agents,[27] although
they were unable to culture the organism from the blood, stool or
joint fluid.   Anhemolytic streptococci have been found on blood culture,[4v]
and the enterococcus has been held responsible by others.[4y]   Atypical
spirochetes were found in the blood by Reiter[28] and in the urethral
discharge by Macfie.[3]

The most promising bacteriologic work has been done by Dienes,[29]
who cultured pleuropneumonia-like organisms from the urethra of a
man suffering from urethritis and arthritis.   These organisms have
previously been found in rats suffering from arthritis, in the conjunc-
tival sac of normal mice and in agalactia in sheep, a syndrome consist-
ing of conjunctivitis and arthritis and infection of the udders in the
female and of the testes in the male.   They have been cultured from the
vagina of women suffering from leukorrhea and recently from the
urethra of males suffering from nonspecific urethritis.[30]   The organism
is extremely pleomorphic, changes its shape and may reproduce by sexual
and asexual means.   In one form it may be filtered like a virus, and in
another it may lead an intracellular, parasitic existence.   In addition,
forms exist which resemble true bacteria in every way, including growth
requirements.[31]

When the drawings and description of the organisms found by
Reiter[1] and Macfie[3] are compared with the known characteristics of
the pleuropneumonia-like organisms, a striking resemblance is evident,
and suggests the possibility that they are, in fact, identical.

It is difficult to draw any conclusions as to the transmission of the
disease in the general population.   Cases in which diarrhea is present,

27. Fiessinger and Leroy.[2] Besson and Ehringer.[4c] Gounelle, Bohn, Koskas
and Marche.[4d]   Germain and Pirot.[4k]   Hombourger (footnote 4*l* and *m*).
Kruspe.[4r]   Rist.[4c']   Schittenhelm and Schlecht.[4f']   Schittenhelm.[4g']   Worms,
Lesbre and Sourdille.[4p'] Worms and Sourdille.[4q'] Worms, Sourdille and Lesbre.[4r']
Worms, Lesbre and Sourdille.[4s']

28. Reiter (footnotes 1 and 4 *a'* and *b'*).

29. Dienes, L., and Smith, W. E.: Relationship of Pleuropneumonia-like (L)
Organisms to Infections of the Human Genital Tract, Proc. Soc. Exper. Biól. &
Med. **50**:99, 1942.

30. Beveridge, W. I. B.: Isolation of Pleuropneumonia-like Organisms from
the Male Urethra, M. J. Australia **2**:479, 1943.

31. Beeuwkes, H., and Collier, W. A.: Studies on Arthrotropic Pleuropneu-
monia-like Microorganisms, J. Infect. Dis. **70**:1, 1942.   Sabin, A. B.: Filterable
Microorganisms of Pleuropneumonia Group, Bact. Rev. **5**:1, 1941.   Shwartzman,
G:: Some Recent Advances in Bacteriology and Virus Research with Special
Reference to Electron Microscopy, J. Mt. Sinai Hosp. **11**:137, 1944.   Dienes and
Smith.[29] Beveridge.[30]

suggest entrance of the agent through the gastrointestional tract.[32] The causative agent may primarily damage the intestinal wall or may secondarily find a portal of entrance through the damaged mucosa, a mechanism which might be postulated in arthritides following ulcerative colitis and regional ileitis.

The available evidence indicates that in the nondiarrheal cases the genital tract is probably the channel of invasion.[33] The fact that the syndrome has never been reported in women does not eliminate this possibility. It is well known that the female genital tract harbors potentially pathogenic agents which never cause disease in the carrier [34] or cause at most a leukorrhea which is often overlooked or ignored.[4k'] In this connection Kristjansen's experience [4q] is of great interest. In his patient nonspecific urethritis and arthritis developed one week following intercourse with a girl who was known to have a vaginal discharge which was repeatedly found negative for gonococci. She had relations with another man in whom a nonspecific urethritis without arthritis subsequently devoloped.

THERAPY

Practically all available types of medication has been used at one time or another, among them salicylates, arsenicals, mild mercurous chloride, fever therapy and, more recently, sulfonamide compounds and·penicillin, all without success. For patients with gastrointestinal disturbances antidysentery serum has been tried. Usseglio and Zancan [18b] claimed some improvement with therapy with gold preparations. Kardung's [33b] patient was asymptomatic after three months following a course of systemic fever therapy.

SUMMARY

1. A case of Reiter's disease is presented which illustrates the different features of the disease.

2. The earliest symptom is frequently diarrhea followed by urethritis and conjunctivitis and later by migratory polyarthritis. Vesicular and hyperkeratotic cutaneous lesions are often noted. Infrequently bleeding tendencies with disturbances of the bleeding and clotting mechanism occur. Incomplete syndromes have been described.

32. Singer, G.: Die akute rheumatische Polyarthritis als Streptokokkenkrankheit, Med. Klin. **21**:1530, 1925. Pemberton.[24d]

33. (a) Frühwald, R., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 21, p. 487. (b) Kardung: Ein unter dem Bilde der Reiterschen Erkrankung verlaufender Fall von Urethritis, Arthritis und Conjunctivitis, Med. Welt **15**:403, 1941. (c) Beck.[4b] (d) Kristjansen.[4q] Kuske.[4s]

34. Hissard, R., and Husson, P.: Uréthrite vénérienne, subaiguë, bénigne, de nature inconnue, Bull. Soc. franç. der dermat. et syph. **39**:1877, 1932. Frühwald.[33a]

3. The disease occurs exclusively in males, usually in their early twenties.

4. It has been reported from Western Europe, the United States and the Pacific Islands.

5. The cause of the syndrome is obscure; the most likely etiologic agent belongs to the group of the pleuropneumonia-like organisms.

6. The portal of entry is either the gastrointestinal or the urethral tract.

7. The prognosis for life is good. Permanent ocular and joint lesions may occur.

Dr. Frederick Zak helped in the preparation of this paper.

CARDIAC ENLARGEMENT IN FEVER THERAPY INDUCED BY INTRAVENOUS INJECTION OF TYPHOID VACCINE

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THE effects of febrile illnesses on the heart have long been of interest to the physician. The pronounced weakness of the voluntary muscles in patients with infectious diseases suggests the possibility that the myocardium may also be affected. Observations that febrile illnesses rarely produce obvious signs of heart failure in otherwise normal subjects do not indicate that the heart remains unaffected. The myocardium of a normal person can withstand considerable strain and must be greatly injured before it will fail. Patients with infectious diseases are usually forced to remain at rest, and the great reserve of the heart is rarely exhausted. It has been noted, however, that in persons undergoing strenuous physical exertion cardiac enlargement frequently develops after intercurrent illnesses.[1]

In patients with subacute bacterial endocarditis cardiac decompensation has been precipitated by the intravenous injection of typhoid vaccine. We have also observed acute myocardial failure in a patient with induced malaria and hypertensive heart disease. That pneumonia and acute upper respiratory infections may initiate congestive failure in patients with compensated heart disease is well known.

In treating patients with neurosyphilis with fever induced by the intravenous administration of typhoid vaccine we have noted in roentgenographic examination that cardiac enlargement occurred in a significant number of cases. Our observations on this phenomenon constitute the subject of this report.

METHOD OF STUDY

Teleoroentgenograms of the heart were taken on 15 patients preceding fever, following each paroxysm and several weeks after the completion of therapy.

1. Kaufmann, R.: Ueber Herzerweiterungen, Wien. Arch. f. inn. Med. **1**:211, 1920.

In a second group, of 24 patients, teleoroentgenograms were made before fever therapy and several months after its completion. In every repeat examination a special effort was made to obtain roentgenograms with the diaphragms in a position comparable to that of the original film; when this was not possible, the patients were excluded from the study. Deep inspiration was avoided to eliminate an involuntary Valsalva effect.

The size of the heart was determined in each roentgenogram by measuring the transverse diameter, since this seemed to be the simplest and most accurate method of obtaining comparable values. In normal patients the amplitude of the right border of the heart varies from 2 to 3 mm. and that of the left border from 3 to 5 mm.[2] Changes in the transverse diameter, less than 8 mm., therefore, were not considered significant in this study.

Electrocardiograms were taken frequently during the course of fever on 15 patients. Determinations of plasma protein were performed at weekly intervals by the falling drop method.[3] In 8 patients hepatic function was studied by the intravenous hippuric acid test before and after fever therapy. The right atrial pressure and the cardiac output were determined by the indwelling venous catheter technic on 8 patients at the completion of fever therapy.[4] Hematocrit readings and measurements of plasma volume were made before and after treatment in this group. The plasma volume was measured by the injection of the blue dye T 1824.[5] The concentration of dye was determined in a sample of serum obtained ten minutes after the injection of the dye.

Our method of producing hyperpyrexia in the treatment of neurosyphilis has been described in detail elsewhere.[6] In brief, the procedure consists in the administration of a series of continuous intravenous infusions of typhoid vaccine. A single treatment consists of approximately eight hours of fever (temperature 104 to 105 F.). Gradually increasing quantities of typhoid vaccine are given on alternating days until fifty hours of fever with temperatures above 103 F. are obtained. Temperatures higher than 106 F. are avoided whenever possible. · During the febrile period not more than 4,000 cc. of fluid is given parenterally, half of which usually consists of isotonic solution of sodium chloride. Tolerance to the vaccine develops rapidly, and approximately 50,000,000,000 organisms are required to obtain a satisfactory febrile response by the time fever therapy is completed. The patients receive the regular hospital diet without additional vitamins or nourishment. During the febrile periods the patients are confined to bed, but they are ambulatory on the intervening days.

2. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943.

3. Barbour, H. G., and Hamilton, W. F.: Blood Specific Gravity: Its Significance and a New Method for Its Determination, Am. J. Physiol. **69:**654, 1924.

4. Cournand, A.; Riley, R. L.; Breed, E. S.; Baldwin, de F., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle, J. Clin. Investigation **24:**106, 1945.

5. Gibson, J. G., II., and Evelyn, K. A.: Clinical Studies of the Blood Volume: IV. Adaptation of the Method to the Photoelectric Microcolorimeter, J. Clin. Investigation **17:**153, 1938.

6. Heyman, A.: The Treatment of Neurosyphilis by Continuous Infusion of Typhoid Vaccine, Ven. Dis. Inform. **26:**51, 1945.

RESULTS

The results of the roentgenologic and laboratory studies on 15 patients during the period of fever therapy are shown in the table. Cardiac enlargement was noted in 8 cases, with increases in transverse diameter varying from 1 to 2.3 cm. (fig. 1 and 2). In 2 patients there was an associated pulmonary congestion, and in 2 others small areas of atelectasis developed. In 7 patients no significant enlargement of the heart was noted.

Only 1 patient (J. C., patient 3) was thought to have had preexisting heart disease. He gave a history of exposure to welding fumes, and the roentgenogram of the chest showed evidence of pulmonary fibrosis and slight prominence of the pulmonary artery. There were no murmurs, and the electrocardiogram showed right axis deviation. A diagnosis of early cor pulmonale was made.

The increase in size of the heart was usually recognized by the end of the first week, but it was more pronounced after the second or third week of therapy. Regression of the cardiac enlargement usually occurred during the month following fever.

In 9 of the 15 cases transient electrocardiographic changes were noted. These changes were slight, and they usually consisted of inversion of T waves or of slight elevation of the ST segment. No evidence of severe or permanent myocardial damage was noted. Following fever therapy a few rales were sometimes heard at the base of the lungs but these usually disappeared spontaneously. No changes were noted on auscultation of the heart. Pedal edema appeared occasionally after the patient left the hospital, but this was thought to be the result of hypoproteinemia. The majority of patients lost from 1 to 8 pounds (0.5 to 3.6 Kg.) in weight during the course of fever therapy. Five patients, however, gained from 3 to 6 pounds (1.4 to 2.7 Kg.).

The hemoglobin concentration and the hematocrit reading usually showed a pronounced fall. The changes in blood volume of the patients in whom cardiac enlargement developed were not consistent. Three of these patients showed increased blood volume, while the remaining patients showed decreased volume. The cardiac output and cardiac index were determined at the completion of fever therapy on 8 patients and were found to be within normal limits. One of these patients (patient 8) had an increase in atrial pressure.

The plasma protein levels were determined on 14 patients; the level was slightly elevated in 3 and significantly lowered in 11 patients. The hippuric acid excretion test showed impairment of hepatic function following fever therapy in 3 of the 8 patients tested.

In the second group of patients (24), teleoroentgenograms were obtained from three to twelve months after fever therapy was completed

Summary of Data for Fifteen Patients Before and After Fever Therapy

Patient No.	Initials	Age, Yr.	Sex	Race	Type of Neurosyphilis	Transverse Diameter of Heart, Cm.			Total Protein, Gm./100 Cc.		Hippuric Acid Test, Gm. Equivalent Benzoic Acid		Hematocrit, %		Blood Volume, Cc./Sq. M.		Cardiac Output, L./Min. After Fever	Cardiac Index, L./Min./Sq. M. After Fever	Electrocardiographic Changes
						Before Fever	After Fever	Change	Before Fever	After Fever	Before Fever	After Fever	Before Fever	After Fever	Before Fever	After Fever			
1	M. S.	30	F	N	Dementia paralytica	11.3	13.6	2.3	7.6	5.7	....	....	41.4	27.5	2,500	2,700	4.0	2.76	Inversion of T3
2	B. B.	25	M	W	Dementia paralytica	10.8	12.9	2.1	6.7	3.9	....	....	....	....	.....	.....	...	....	No change
3	J. C.	38	M	W	Optic atrophy	11.2	12.8	1.6	6.3	4.6	0.55	0.69	49.6	44.2	2,967	2,600	7.9	4.6	Slight elevation of ST3
4	L. K.	39	F	N	Optic atrophy	11.3	12.7	1.4	..	..	....	....	....	....	.....	.....	..	....	
5	J. C.	34	M	W	Tabes dorsalis	12.9	14.2	1.3	5.1	4.0	....	....	42.2	36.2	3,160	3,730	10.4	6.0	No change
6	G. A.	32	F	W	Asymptomatic	11.3	12.3	1.0	5.7	6.3	....	....	....	....	.....	.....	..	....	Inversion of T2 and T3
7	H. H.	40	M	N	Asymptomatic	13.8	14.8	1.0	6.8	7.3	....	....	....	....	.....	.....	..	....	No change
8	M. J.	27	F	N	Dementia paralytica	11.7	12.7	1.0	6.4	4.6	0.01	0.08	35.5	23.8	2,320	3,190	4.1	2.9	T1 and T2 became isoelectric
9	H. M.	34	M	N	Asymptomatic	16.2	17.0	0.8	5.4	4.2	0.80	0.24	47.9	41.0	3,520	3,380	6.4	3.5	Decreased voltage of T1 and T2
10	A. O.	27	F	N	Asymptomatic	14.5	14.7	0.2	5.8	5.1	0.93	0.75	41.4	33.0	2,300	2,540	5.5	3.5	No change
11	A. G.	30	F	N	Asymptomatic	9.7	9.5	0.2	6.0	4.8	0.59	0.72	34.6	22.9	2,100	2,600	5.4	3.6	No change
12	L. M.	36	F	N	Asymptomatic	13.1	13.2	0.1	7.5	5.8	....	....	....	....	.....	.....	..	....	Intraventricular conduction time increased to 0.08 second
13	A. F.	24	M	N	Asymptomatic	14.6	14.7	0.1	6.3	6.8	0.93	0.92	....	....	.....	.....	..	....	Changed to left axis deviation
14	M. P.	15	F	N	Optic atrophy	10.1	10.1	...	6.6	5.5	0.68	0.40	41.9	32.3	2,100	2,100	..	....	Inversion of T3
15	F. G.	20	M	N	Asymptomatic	12.2	12.2	...	6.7	5.7	1.0	0.50	43.5	38.5	2,200	2,500	4.95	3.1	Inversion of T3; elevated ST1 and ST2

and compared with those made before treatment. The heart was found to be larger in 4 patients, all of whom had had fever therapy within the preceding six months. In 4 additional cases definite cardiac enlargement was also present, but as these patients had gained considerable
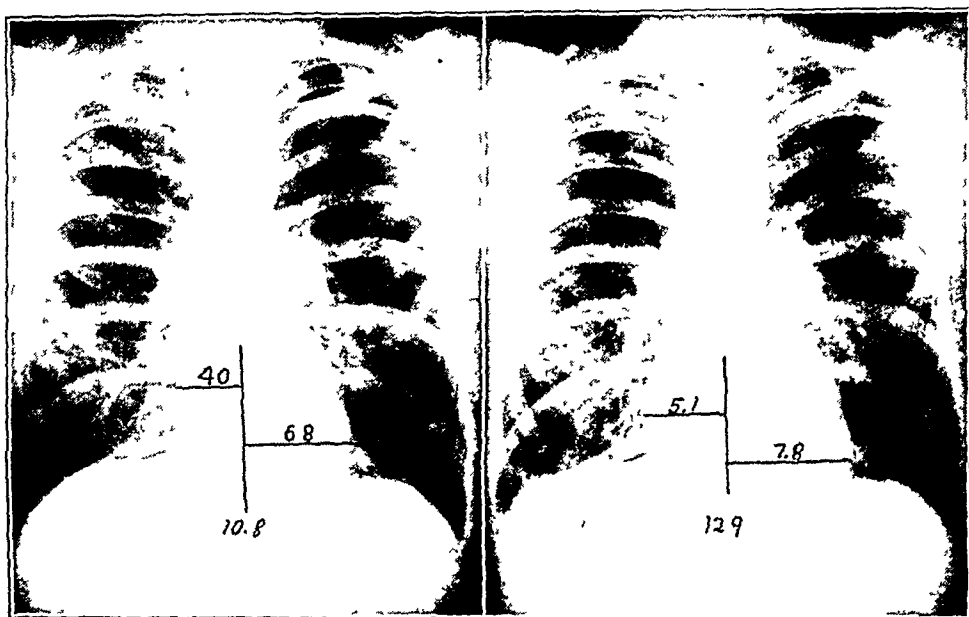
Fig. 1 (patient 2).—Cardiac enlargement. Roentgenograms of the chest taken before and after fever therapy. Note the small area of atelectasis in the base of the right lung.
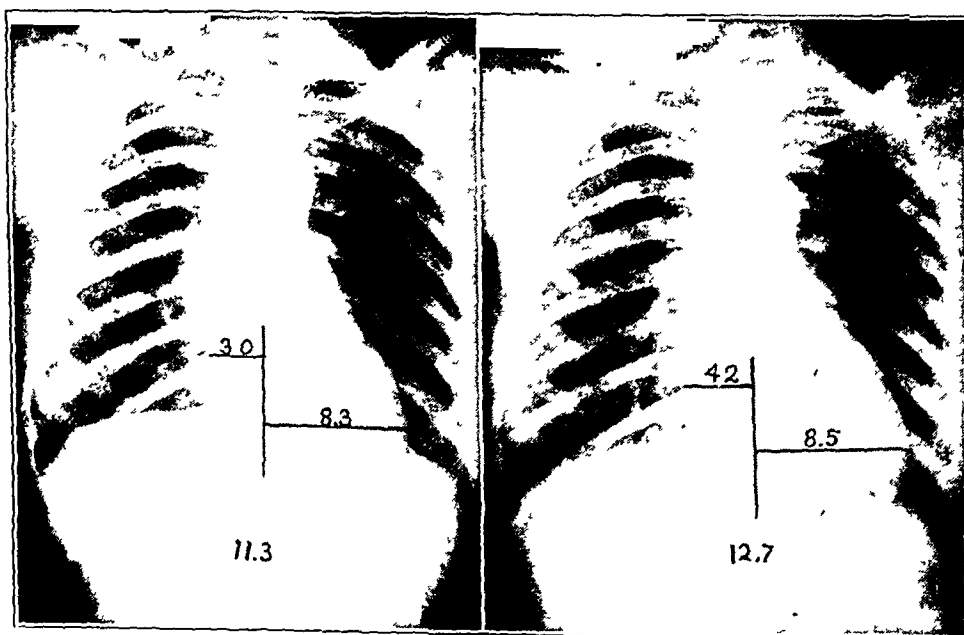
Fig. 2 (patient 4).—Cardiac enlargement. Roentgenograms of the chest taken before and after fever therapy.

weight the changes in heart size could not be evaluated. The remaining 16 patients showed no change in the cardiac silhouette. In no instance was the heart significantly smaller than before fever therapy.

COMMENT

The enlargement of the transverse diameter of the heart of 1 cm. or more represents a considerable increase in the total volume of the heart. An increase of only 0.5 cm. in transverse diameter of an average-sized heart has been shown to produce a 13 per cent increase in cardiac volume.[7]

Fever and febrile illnesses have for a long time been thought to exert a damaging effect on the heart. Thayer[8] found that 12 of 188 patients with typhoid fever had an increase in size of the heart on percussion three months to fourteen years after recovery from this infection. In a study of changes in the size of the heart in pneumonia Levy[9] noted that 60 per cent of the patients had roentgenographic evidence of cardiac enlargement during this infection. Both pneumonia and typhoid are known to produce histologic changes in the myocardium, and electrocardiographic abnormalities have also been noted during these infections.[10] In animal experiments myocardial degeneration has been observed following artificial fever; in human beings, severe and permanent electrocardiographic changes have occurred during artificial fever therapy.[11]

Despite these observations, little attention is generally paid to cardiac function in those febrile illnesses not primarily involving the heart. Since fever and febrile infections may exert a deleterious influence on the heart, their effects cannot be ignored.

The factors causing cardiac enlargement during febrile diseases have not been determined, and the few reports relative to this problem deal with avitaminosis or infections, such as diphtheria, which are known to affect the heart. Other possible sources of cardiac enlargement are: an increase in blood volume associated with acute infections; additional

7. Jonsell, S.: A Method for the Determination of the Heart Size by Teleo-roentgenography, Acta radiol. **20**:325, 1939.

8. Thayer, W. S.: The Late Effects of Typhoid Fever on the Heart and Vessels, Am. J. M. Sc. **127**:391, 1904.

9. Levy, R. L.: The Size of the Heart in Pneumonia: A Teleroentgeno-graphic Study, with Observations on the Effect of Digitalis Therapy, Arch. Int. Med. **32**:359 (Sept.) 1923.

10. Stone, W. J.: The Heart Muscle Changes in Pneumonia, with Remarks on Digitalis Therapy, Am. J. M. Sc. **163**:659, 1922. Master, A. M., and Romanoff, A.: Electrocardiographic Changes in Pneumonia, Proc. Soc. Exper. Biol. & Med. **28**: 266, 1930. Brow, G. R.: The Heart in Typhoid Fever, Canad. M. A. J. **20**:606, 1929.

11. Haam, E., and Frost, T. T.: Changes in the Parenchymatous Organs, Produced by Artificially Induced Fever, Proc. Soc. Exper. Biol. & Med. **42**:99, 1939. Harvey, A. M., and Billings, F. T.: Coronary Occlusion After Fever Therapy for Sulfonamide-Resistant Gonorrheal Urethritis, Am. Heart J. **29**:205, 1945.

work placed on the heart by the heightened metabolism in fever; and, finally, direct injury to the myocardium produced by the infectious agent.

Influence of Blood Volume on Size of the Heart.—It has recently been suggested that cardiac failure in pneumonia or other infections is due in part to the increase in blood volume which has been described during these illnesses.[12] In view of the large quantities of fluids given parenterally to our patients undergoing fever therapy, this factor becomes of considerable interest. The effect of the circulating blood volume on cardiac size has been observed in a variety of diseases. The size of the heart is reduced in shock caused by decreased blood volume, and similar changes have been noted associated with acute hemorrhage.[13] The decreased size of the heart in Addison's disease has been attributed partly to the lower plasma volume occurring in this condition. As the blood volume is restored by the use of desoxycorticosterone in Addison's disease, the heart returns to its normal size. Occasionally an excess of desoxycorticosterone results in cardiac enlargement and pulmonary congestion.[14]

It was thought at first that a similar mechanism may have existed in our patients and that the enlargement of the heart was a result of an increased blood volume. Our studies failed to support this concept. The blood volume was slightly increased in almost every patient following fever, but there appeared to be no correlation between this fact and the changes in size of the heart.

In connection with this study, observations were made on 2 normal subjects as to the possible variation in cardiac size produced by sudden changes in venous pressure and by a rapid elevation of blood volume. The venous pressure and right atrial pressure were first lowered by the application of venous tourniquets to the thighs, and roentgenograms of the heart were made. The tourniquets were then released and 1,000 cc. of a 5 per cent solution of human albumin was given intravenously through a large bore needle and the roentgenograms of the heart repeated.

The application of venous tourniquets to the thighs would be expected to lower the atrial pressure by approximately 40 mm. of water. The

12. Rutstein, D. D.; Thomson, K. J.; Tolmach, D. M.; Walker, W. H., and Floody, R. J.: Plasma Volume and Extravascular Thiocyanate Space in Pneumococcus Pneumonia, J. Clin. Investigation **24**:11, 1945.

13. (*a*) Kondo, B., and Katz, L. N.: Heart Size in Shock Produced by Venous Occlusion of the Hind Limbs of the Dog, Am. J. Physiol. **143**:77, 1945. (*b*) Meek, W. J.: The Use of X-Rays in the Study of Physiology, Radiology **8**:369, 1927.

14. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113**:1725 (Nov. 4) 1939.

rapid infusion of albumin would raise the atrial pressure approximately 100 mm. of water above the resting level. Thus the change in atrial pressure between the two roentgenographic examinations would be 140 mm. of water.[15]

As estimated from the change in hemoglobin concentration, the albumin had increased the blood volume by 1,150 cc. in subject 1 and by 1,000 cc. in subject 2 at the time the second films were taken. The change in venous pressure of 150 mm. of water and the increase of 1 liter in blood volume caused no significant increase in the size of the heart. In similar experiments on animals extremely large quantities of fluid by the parenteral route were necessary before cardiac enlargement occurred.[13b]

In the experiments recorded there was no change in the extracellular fluid volume, the entire change occurring in the atrial pressure and in the blood volume. It may be that an increase in blood volume associated with an increase in extracellular fluid volume would cause cardiac enlargement. This problem warrants further investigation.

It seems unlikely that the cardiac enlargement found in patients with febrile illnesses or in those undergoing fever therapy is caused exclusively by the relatively small increase of blood volume associated with these conditions. Further evidence against this possibility is the persistence in a few of our cases of cardiac enlargement for as long as several months, for usually the increase in blood volume produced by infections is temporary. [12]

Cardiac Work Produced by Fever.—The increase in metabolism produced by fever is to some extent covered by an increase in cardiac work. This factor must be taken into consideration, for increased work of the heart is known—in some athletes, for example—to produce enlargement. The few available reports on cardiac output during fever reveal that there is but little increase in cardiac output during fever or febrile infections.[16] In hyperpyrexia induced by short radio waves there is evidence that the cardiac output is definitely increased.[17] The influence of radiothermy on the circulation, however, is considerably different from that of other forms of fever, and a comparison of their effects on the cardiac output is not justified.[18]

15. Stead, E. A., Jr., and Warren, J. V.: Unpublished data.

16. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C Thomas, Publisher, 1932.

17. Kissin, M., and Bierman, W.: Influence of Hyperpyrexia on Velocity of Blood Flow, Proc. Soc. Exper. Biol. & Med. **30**:527, 1933.

18. Wiggers, C. H., and Orias, O.: The Circulatory Changes During Hyperthermia Produced by Short Radio Waves (Radiothermia), Am. J. Physiol. **100**: 614, 1932.

Nutritional Deficiency.—The possibility exists that the cardiac changes occurring in patients with febrile illness may be the result of nutritional disturbances. Our patients and persons with acute infections take little nourishment during the febrile period. As would be anticipated, considerable effect on both nitrogen balance and vitamin requirements occurs in these circumstances.

The increased utilization of proteins in febrile states is well known, and in some of our patients depletion of plasma proteins sufficient to produce edema developed. Depletion of protein in the body is known to produce dysfunction of many tissues, and it seems possible that the myocardium is also influenced by the destruction of protein in fever. The impairment of hepatic function in 3 patients in this series is of particular interest in this connection.

The increased metabolism in fever is associated with a greater vitamin requirement. It is possible that in our patients and in many of those with febrile infections, vitamin deficiencies similar to beriberi may develop. The onset of cardiac enlargement in our cases was relatively rapid, usually within the first week, and regression occurred without specific vitamin therapy. This seems to be evidence against avitaminosis as an important causative factor. It remains necessary, however, to study the effects of fever on patients having an adequate vitamin and protein intake.

Anemia.—In many persons with febrile conditions and in our patients undergoing fever therapy there is a decrease in the hemoglobin content and red blood cell count. Anemia is known to produce an added burden on the circulation and an increase in cardiac size. It is doubtful, however, whether the degree of anemia observed in our patients could play a predominant part in the production of cardiac enlargement.

Effect of Bacteria on Cell Metabolism.—It has been believed for a long time that cardiac failure in acute infections was due to direct injury to the myocardium produced by the infectious agent. It is conceivable, for instance, that the large quantities of typhoid vaccine used to produce fever in our patients may adversely affect the metabolism of the cardiac muscle. At the present time there is little information on this particular subject. Study of artificial fever therapy is indicated to determine whether cardiac enlargement is peculiar only to bacterial infections.

It may be that no one factor is entirely responsible for the cardiac enlargement observed in our patients. An increase in the blood volume by excessive parenteral administration of fluid, for example, produces little change in the normal heart. However, pulmonary congestion and cardiac failure have been noted following the parenteral administration of fluids to patients after operation or to those ill with acute infections. Similarly, it has been observed that in soldiers without preexisting heart disease cardiac enlargement was not likely to develop as a result

of physical exertion unless they were subjected to intercurrent infections.[1] It has also been shown that cardiac enlargement in beriberi occurs more often in those patients who have undergone physical stress.[19] Beriberi heart is also often precipitated by febrile illnesses. These clinical observations are of considerable importance and indicate the need for more intensive study of the effect of febrile illness on the heart.

SUMMARY

Enlargement of the heart has been noted by roentgenographic examination to occur during fever therapy in 8 of 15 patients with neurosyphilis. Roentgenograms of the heart were obtained on 24 additional patients who had undergone fever therapy during the preceding twelve months. In 4 of these patients, cardiac enlargement was present for as long as six months following hyperpyrexia.

Electrocardiographic studies and determinations of cardiac output, blood proteins and hemoglobin revealed no significant differences between the patients in whom cardiac enlargement developed and those without changes in size of the heart.

In our patients there appeared to be no relationship between the increase in cardiac size and the changes in blood volume. Evidence is produced to show that in normal subjects a rapid and significant increase in the circulating blood volume had no influence on cardiac size.

None of the factors known to influence cardiac size, such as anemia, nutritional deficiency or overwork of the heart, was thought to be the sole cause of the cardiac enlargement.

The observation that fever therapy produces an enlargement of the heart is of interest not only in the treatment of neurosyphilis but also in the consideration of the effects of febrile illnesses on cardiac function. The use of fever therapy provides an opportunity to study these effects under controlled conditions, and suggestions as to further investigation of this problem are offered.

19. Aalsmeer, W. C., and Wenckebach, K. F.: Herz und Kreislauf bei der Beriberi Krankheit, Wien. Arch. f. inn. Med. **16**:193, 1929.

RHEUMATIC FEVER IN NAVAL ENLISTED PERSONNEL

I. An Analysis of the Major Manifestations Observed, the Factors Involved in Its Occurrence and the Cardiac Residua

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TWO hundred and twenty-one cases of rheumatic fever and rheumatic heart disease observed in this hospital have been analyzed in order to determine the significant factors involved in the occurrence of rheumatic fever in naval personnel, the clinical characteristics of the disease and the effectiveness of intensive salicylate therapy. The factors involved in its occurrence, the major manifestations observed and the incidence of permanent cardiac damage will be considered in this paper.

A significant difference exists between military and civilian population groups affected by rheumatic fever. The average age of onset in civilian life is 8 years, and 70 per cent of the persons affected have already acquired the disease by the age of 15.[1] A study of 1,000 cases followed for ten years by Bland and Jones [2] clearly indicates the outlook in this childhood group. The average age of onset was 8 years. Ten years later, at an average age of 18, when these persons would be acceptable for enlistment in the armed forces, 24 per cent were dead, 42 per cent showed varying degrees of permanent cardiac damage and only 31 per cent were free from cardiac lesions. Roughly, then, only 3 out of every 7 persons who have survived childhood rheumatic fever will be acceptable for military service.

No adequate information is available concerning the number of men with a childhood history of rheumatic fever serving in the armed forces. Master [3] found an incidence of 2 per cent among 432 surgical patients in a naval hospital. Two hundred neuropsychiatric patients questioned in this hospital by me revealed an incidence of 0.5 per cent. Delaney,

1. (a) Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease: A Statistical Study, J.A.M.A. **121**:1-8 (Jan. 2) 1943. (b) Coombs, C. F.: Rheumatic Heart Disease, Bristol, John Wright & Sons, Ltd., 1924.

2. Bland, E. F., and Jones, T. D.: Fatal Rheumatic Fever, Arch. Int. Med. **61**: 161-171 (Feb.) 1938.

3. Master, A. M.: The Problem of Rheumatic Fever in the Navy, Am. Heart J. **27**:634-640 (May) 1944.

Miller, Kimbro and Bishop [4] found 100 cases of valvular heart disease among 45,000 men examined for the Army Air Forces, all of whom had previously been screened by physical examination.

It may be assumed that between 5 and 20 men per thousand in the armed forces have had rheumatic fever before enlistment and that approximately 2 per thousand have rheumatic heart disease which existed prior to enlistment. With the exception of this small minority, service personnel should represent a population group from which persons highly susceptible to rheumatic fever have been eliminated.

MATERIAL AND METHODS

The 221 cases analyzed represent the consecutive patients with rheumatic fever and rheumatic heart disease admitted to a northwest naval hospital from December 1943 to April 1945. All patients admitted since January 1944 were under my direct supervision.

The case material was drawn from the Pacific Northwest and from evacuees from the Alaska-Aleutian, Central Pacific and South Pacific areas. Because of rapid movements of troops a patient's illness often had its inception in another geographic area, and the clinical data have been corrected accordingly. The home location of each patient represents the geographic area in which the maximum childhood and adolescent years were spent.

TABLE 1.—*Incidence of Cardiac Systolic Murmurs in One Hundred Neuropsychiatric Patients Considered as a Normal Control Group*

Apical Murmurs	Per Cent
Very slight systolic not transmitted......................................	10
Slight systolic transmitted to anterior axillary line or farther.........	4
Basilar Murmurs	
Very slight systolic not transmitted......................................	4
Slight systolic transmitted to neck......................................	10
Slight systolic not transmitted...	2

The assumption that rheumatic fever existed prior to enlistment is based on a definite history of growing pains with associated cardiac involvement, polyarticular arthritis, rheumatic carditis or chorea. Histories in all instances were obtained solely from the patient.

Cardiac murmurs were recorded as very slight, slight, moderate and loud. Mitral systolic murmurs were evaluated with the patient in the horizontal position and lying on the left side. One hundred neuropsychiatric patients, representing the same age groups, were examined under identical conditions in order to establish standards of expectancy for murmurs in normal persons. The results are presented in table 1. Only slight and very slight systolic murmurs were heard in this group. Slight mitral systolic murmurs transmitted to or beyond the anterior axillary line were found in 4 per cent, and no moderate mitral murmurs were heard.

4. Delaney, J. H.; Miller, S. I.; Kimbro, R. W., and Bishop, L. F., Jr.: Valvular Heart Disease Previously Unrecognized in Military Medical Examinations, J. A. M. A. **123**:884-886 (Dec. 4,) 1943.

Electrocardiograms were taken at weekly intervals. Deviations from normal were based on the criteria adopted by the American Heart Association. Blood sedimentation rates were determined twice weekly by the Cutler technic. A fall of 10 mm. or less in one hour was regarded as normal.

Patients with active rheumatic fever in this hospital were treated in most instances by the intensive salicylate method of Coburn.[5] Information is not available regarding prior treatment received by evacuees while at other hospitals; hence the possible influence of therapeutic procedures on the data to be presented is unknown.

Patients were kept under observation in this hospital until the rheumatic infection was quiescent or until chronic infection had persisted for more than three months. The shortest period of observation in cases of active disease was twenty-nine days, the longest two hundred and eighty-four days and the average fifty-eight days.

PRESENTATION OF DATA

1. *Clinical Manifestations of Rheumatic Fever Observed in Service Personnel.*—The major clinically recognizable manifestations of rheumatic fever consist of polyarticular arthritis, pains in the joints, chorea,

TABLE 2.—*Major Rheumatic Manifestations Exhibited in Two Hundred and Twenty-One Patients Consecutively Admitted for Rheumatic Fever and Rheumatic Heart Disease*

Group	Rheumatic Manifestations Observed	Cases No.	Cases %	Antecedent History of Rheumatic Fever
I	Acute polyarticular arthritis with or without associated recognizable cardiac involvement	157	71.0	56 cases, preenlistment rheumatic fever; 1 case, preenlistment rheumatic fever and chorea; 13 cases, previous rheumatic fever in service but not prior to enlistment
II	Acute polyarthritis and Sydenham's chorea	1	0.4	Preenlistment rheumatic fever and chorea
III	Rheumatic heart disease and concurrent nondisabling pains in joints	12	5.4	6 cases, preenlistment rheumatic fever
IV	Rheumatic heart disease and concurrent chronic polyarthritis	5	2.0	Inception of rheumatic fever in childhood in all 5
V	Rheumatic carditis without other manifestations of rheumatic fever	10	4.6	No previous rheumatic fever
VI	Rheumatic valvular heart disease	36	16.6	14 cases, preenlistment rheumatic fever; 1 case, preenlistment and service rheumatic fever; 2 cases, rheumatic fever in service but not prior to enlistment

valvular heart disease and carditis. In order correctly to evaluate the rheumatic fever problem as it exists in military personnel, it is necessary to establish the character and the incidence of these manifestations. This information, based on the 221 cases of rheumatic fever and rheumatic heart disease, is presented in table 2. One hundred and fifty-eight patients (groups I and II), or 71.4 per cent,[1] of whom had concurrent

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5. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: Rational Technique. Bull. Johns Hopkins Hosp. **73**:435-464 (Dec.) 1943.

Sydenham's chorea, exhibited acute polyarticular arthritis with or without cardiac involvement. An additional 17 patients (groups III and IV), or 7.4 per cent, exhibited articular manifestations in conjunction with rheumatic heart disease. The 5 patients (group IV) with chronic polyarthritis had articular manifestations of sufficient severity to necessitate hospitalization, but in some instances the diagnosis of rheumatic fever would not have been made except for the coexistent heart disease. The 12 patients (group III) with nondisabling pain in the joint represent a group who in many instances would either have remained on a duty status or have been disposed of in nonrheumatic fever wards except for the concurrent cardiac involvement. Therefore, the service incidence of chronic polyarthritis and nondisabling pain in the joint due to rheumatic fever is undoubtedly higher than the 7.4 per cent indicated in table 2, but a more accurate estimate cannot be established.

Most men with valvular heart disease were eliminated by enlistment physical examinations. Therefore, the incidence of 16.6 per cent is much lower than the 47 per cent observed by Cohn and Lingg [1a] in civilians of the same age group. In view of the fact that 40 per cent of these patients had experienced rheumatic fever prior to enlistment and that an appreciable number gave a history of heart disease prior to enlistment, the majority undoubtedly had their disease prior to enlistment and the cases do not represent instances of rheumatic fever acquired in service.

The incidence of carditis alone, without the other manifestations of rheumatic fever, was only 4.6 per cent, which coincides with the observations of Cohn and Lingg [1a] on civilians of the same age group. One patient had acute fulminating carditis and died on the fourth day of hospitalization. The remainder of the patients exhibited rheumatic fever of a relatively low grade activity which led to variable degrees of significant cardiac damage.

The tabulated data clearly indicate that the problem of rheumatic fever in service personnel consists primarily of the prevention, recognition and treatment of a disease which begins as acute polyarticular arthritis in at least 71 per cent of the cases and produces articular manifestations of some kind in over 79 per cent. Therefore, an analysis of the 158 cases (groups I and II) of acute polyarthritis observed during the acute, subsiding or convalescent phase, offered the best approach to the problem. The remainder of the clinical data are derived from this group.

2. *Preenlistment Rheumatic Fever.*—Forty-eight, or 36 per cent, of the group of 158 patients gave a history of rheumatic fever prior to enlistment. Of this number, 34 had had a single polyarticular episode, while 24 gave a history of two or more attacks. Nine of the latter group suffered from recurrent painful, and at times swollen, joints as often as two or three times a winter and/or from chronic residual pain

in the joints. One patient gave a history of chorea in addition to multiple attacks of polyarthritis.

Table 3 shows the age of onset in these patients. Seventy-one per cent had acquired the disease by the age of 15, which coincides with the general experience in civilian population groups.[1]

TABLE 3.—*Age at Beginning of Initial Attack of Fifty-Eight Patients Who Had Experienced Rheumatic Fever Prior to Enlistment*

Age, Years	Number of Cases	Per Cent Before and After Age 15
1- 5	5	
6-10	18	71
11-15	18	
16-20	13	
21-25	3	29
26-30	1	

The latent period between the last attack in civilian life and the first recrudescence in service is shown in table 4. If the 9 patients with chronic rheumatic infection are excluded, the latent period was more than five years in 67 per cent.

TABLE 4.—*Latent Period Before the Onset of the First Service Attack of Rheumatic Fever in Forty-Nine Patients Who Had Experienced Preenlistment Infection*

Latent Period, Years	Number of Cases *	Per Cent with Interval Less Than or More Than 6 Years
1- 5	16	33
6-10	19	
11-15	8	
16-20	4	67
21-30	2	

* Nine patients who experienced recurrent painful joints following the initial attack have been omitted.

3. *Preenlistment Home Area of Patients and Geographic Area in Which This Attack Began.*—The home areas of the patients who had a history of rheumatic fever prior to enlistment and those whose first attack began in service are presented in table 5. The influence of the location of this hospital in the Pacific Northwest is apparent in the data. Nevertheless, all sections of the country are represented. An appreciable number of the patients contracted preenlistment rheumatic fever in the Southeast and Southwest population areas, where the incidence of rheumatic fever is regarded as low.[6]

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6. (a) Swift, H. F.: Public Health Aspects of Rheumatic Heart Disease, J. A. M. A. **115**:1509-1518 (Nov. 2) 1940. (b) Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931

Fifty-one per cent had lived in towns and rural and semirural areas, while 49 per cent lived in cities. The city-bred patients, better adjusted to the epidemiologic hazards of crowding, were as susceptible to service rheumatic fever as those from towns and rural and semirural areas.

The geographic area in which their attacks began is shown in table 6. The majority began in the Pacific Northwest. Nevertheless, all sections of the country were represented. A significant number contracted their initial infection or suffered recrudescence of quiescent infections

TABLE 5.—*Home Location of One Hundred and Fifty-Eight Patients with Rheumatic Fever*

Geographic Area of Home Location	First Attack Antedated Enlistment	First Attack in Service	Total
Northeast states..............	7	9	16
Southeast states..................................	8	12	20
North-Central states.......	5	12	17
Central states....................................	17	28	45
Northwest states..................................	11	22	33
Southwest states.................................	10	17	27
Total......................................	58	100	158

TABLE 6.—*Geographic Area in Which This Attack of Rheumatic Fever Began*

Geographic Area in Which This Attack Began	Patients with Previous Rheumatic Fever	Patients Without Previous Rheumatic Fever	Total
Northeast states................................	2	3	5
Southeast states.................................	1	0	1
Central states...................................	2	1	3
Southwest states................................	5	6	11
Northwest states................................	43	59	102
Alaska-Aleutian area............................	8	11	19
Central Pacific area..............................	9	6	15
South Pacific area...............................	1	1	2
Total......................................	71	87	158

in the Southwest, principally in San Diego, and in tropical areas where the incidence of rheumatic fever in civilian population groups is only one-fifth to one-fifteenth as common as in temperate zones of the United States.[7] In only 1 case was the disease incurred under the hardships of combat, which parallels observations from World War I that rheumatic fever occurred commonly in barracks-quartered troops but infrequently in troops in the field under combat conditions.[1b]

(c) Hedley, O. F.: Trends, Geographical and Racial Distribution of Mortality from Heart Disease Among Persons from 5-24 Years of Age in the United States During Recent Years (1922-1936), Pub. Health Rep. **54:**2271-2297 (Dec. 29) 1939.

7. (a) Clarke, J. T.: Geographical Distribution of Rheumatic Fever, J. Trop. Med. **33:**249-258 (Sept. 1) 1930. (b) White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937.

4. *Age when This Attack Began, Length of Service and Hereditary Factors.*—The age of onset of this attack is presented in chart 1.

The youngest patients were 17 years of age, and the oldest patient was 60. Forty-nine per cent were 18 to 20, which likewise represents the enlistment age of most recruits at the time of this study.

Chart 2 show the duration of service before this attack began.
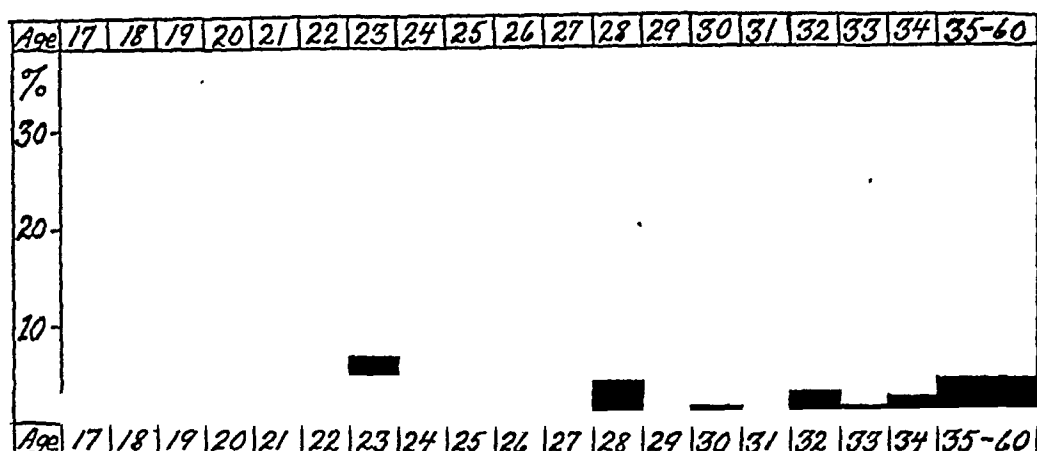
Chart 1.—Age at onset of the present attack of rheumatic fever (158 cases).
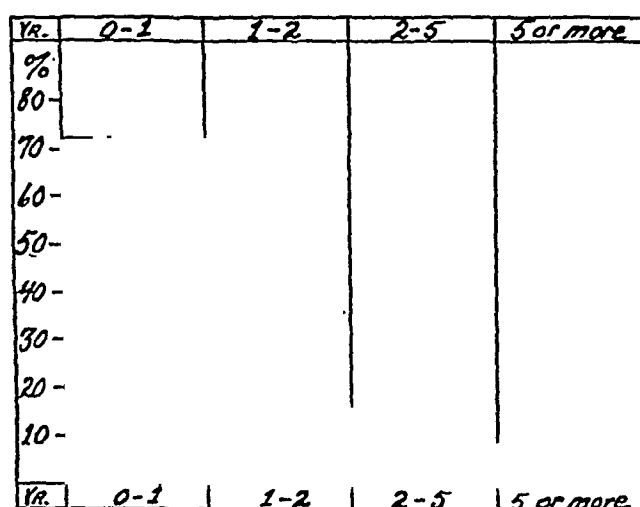
Chart 2.—Length of service before the beginning of the present attack of rheumatic fever (158 cases).

Since none of the patients who require hospitalization at primary training stations are admitted to this hospital, the number who contract rheumatic fever within the first year of service is actually higher than the 72 per cent occurrence rate shown in chart 2. Coburn [8] found that in 80 per cent of his cases the disease occurred in the first year. There-

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8. Coburn, A. F.: The Management of Navy Personnel with Rheumatic Fever, U. S. Nav. M. Bull. **41**:1324-1328 (Sept.) 1943.

fore the high incidence of rheumatic fever in the 18 to 20 year old patients can be interpreted not as indicating unusal susceptibility at this age but, rather, as reflecting certain conditions inherent in the first year of service.

Hereditary factors were of no apparent significance. Only 8 per cent gave a family history of rheumatic fever.

5. *Seasonal Incidence of Rheumatic Fever.*—The seasonal trend under service conditions is presented in chart 3. Cases of patients received at this hospital through May 1945 have been included. The admission rate dropped materially after a large primary training center in the Northwest was closed, in the fall of 1944. Since then, the incidence of infection in early winter months has materially decreased and the seasonal trend more closely parallels the curve observed in civilian
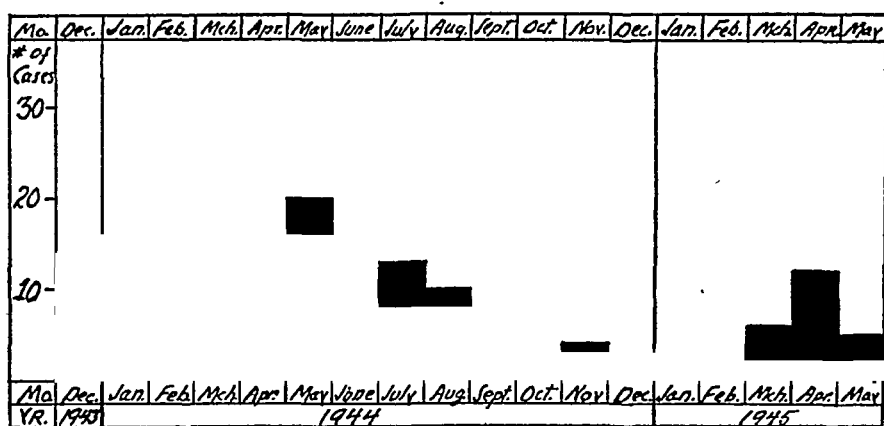
Chart 3.—Seasonal distribution of cases of rheumatic fever from December 1943 to June 1945.

population groups,[7b] with the highest incidence in the late winter and spring months. As observed by others,[9] the service morbidity rate was low during the summer months.

6. *Relation to Antecedent Infections.*—Table 7 clearly demonstrates the striking relationship recognized as existing between antecedent infections of the respiratory tract and acute rheumatic fever in military as well as in civilian populations.[10] Of 81 per cent of patients who gave

9. Wendkos, M. H., and Noll, J., Jr.: A Survey of Rheumatic Fever in a Large Station Hospital, M. Clin. North America **28**:124-147 (Jan.) 1944.

10. (*a*)· Coburn, A. F.: Observations on the Mechanism of Rheumatic Fever, Lancet **2**:1025-1030 (Oct. 31) 1936. (*b*) Jones, T. D., and Mote, J. R.: Clinical Importance of Infection of the Respiratory Tract in Rheumatic Fever, J. A. M. A. **113**:898-902 (Sept. 2) 1939. (*c*) Coburn, A. F.: Epidemiology of Streptococcus Hemolyticus Infections at Naval Training Stations, U. S. Nav. M. Bull. **41**:1012-1018 (July) 1943.

a history of antecedent factors, all except 3 per cent had infections of the respiratory tract, usually attributed to, or complicated by, hemolytic streptococci.

The time interval between the symptomatic onset of antecedent infections and rheumatic fever is shown in table 8. Only those patients

TABLE 7.—*Clinical Character of the Antecedent Illness Considered as Precipitating Rheumatic Fever (One Hundred and Fifty-Eight Cases)*

Antecedent Illness	Incidence, per Cent
Tonsillitis or sore throat alone or accompanied with other manifestations in the upper respiratory tract...	46
Acute catarrhal fever...	16
Cold in the head...	8
Scarlet fever...	5
Nasal infection...	2.5
Otitis media...	0.7
Acute gastroenteritis...	1.4
Exposure...	0.7
Diphtheria...	0.7
No history of antecedent illness...	19

who had a clearly defined onset have been included. An interval of one to three weeks existed in 43 per cent of the cases. In many instances the antecedent infection still persisted when the rheumatic fever began.

TABLE 8.—*Interval Between Symptomatic Onset of the Antecedent Infection of the Respiratory Tract and Rheumatic Fever*

Interval, Weeks	Per Cent of Cases
0-1...	12
1-2...	20
2-3...	23
3-4...	11
4-5...	13
5-6...	3
6-7...	2
7-8...	3
Recurrent infection over a period of 2-4 mo......	13

7. Residual Cardiac Observations.—The residual cardiac observations at the time of discharge from the hospital are presented in table 9. Seven per cent suffered permanent significant cardiac damage from this attack. Twenty-five per cent showed residual, slight or moderate apical systolic murmurs transmitted to or beyond the anterior axillary line, and they were classed as having potential rheumatic heart disease. Sixty-six per cent escaped any evidence of residual damage to the heart. Two patients with previous rheumatic heart disease showed evidence of further cardiac damage. All 13 of the patients who had experienced a previous attack in service but not prior to enlistment escaped residual significant heart disease.

The residual damage suffered from this attack consisted in 8 cases of mitral insufficiency, 4 with and 4 without roentgenic evidence of car-

diac enlargement; in 3 cases, of aortic and mitral insufficiency, 2 with and 1 without cardiac enlargement, and in 1 case of second degree cardiac enlargement with only a moderate mitral systolic murmur transmitted to the axilla. In 3 of the cases of mitral insufficiency there were middiastolic mitral murmurs in addition to the loud systolic murmur characterizing each of these cases. The evidence reported by Bland, White, and Jones[11] indicates that these cases should be classified as instances of mitral insufficiency rather than of early mitral stenosis. Of the 2 patients whose previous heart disease was aggravated, 1 showed mitral stenosis and aortic insufficiency with cardiac enlargement, and the other showed mitral stenosis without cardiac enlargement.

TABLE 9.—*Residual Cardiac Conditions in One Hundred and Fifty-Eight Cases of Acute Rheumatic Fever*

| Group | Number of Patients | Heart Normal, % | Potential Rheumatic Heart Disease | | Perma- nent Cardiac Damage, % | Rheumatic Heart Disease Existing Before This Attack but Aggra- vated by It, % |
			SSM to A,* %	MSMM to A,† %		
Preenlistment rheumatic fever, single attack.........	34	62	12	14	8.5	3.5
Preenlistment rheumatic fever, multiple attacks.....	24	67	8	17	4	4
Previous attack in service but not prior to enlistment	13	77	7	16	...	...
First attack of rheumatic fever.....................	87	65	12	13	8	...
Total..................	158	66	25		7	

* Slight systolic mitral murmur transmitted to or beyond the anterior axillary line.
† Moderate mitral systolic murmur transmitted to or beyond the anterior axillary line.

Abnormal electrocardiograms were encountered in 29, or 26 per cent, of the 113 patients observed during active infection. Fifteen, or 52 per cent, of this group showed no residual evidence of cardiac damage; 7, or 24 per cent, showed potential rheumatic heart disease, and the remaining 7, or 24 per cent, were among those who suffered permanent damage.

COMMENT

The clinical material presented clearly indicates that four major factors are involved in the occurrence of rheumatic fever in service personnel: (1) infections of the respiratory tract due to hemolytic streptococci, (2) length of service, (3) seasonal influences and (4) antecedent rheumatic fever. Seventy-eight per cent. of the patients in this series gave a history of antecedent infection of the respiratory tract. The attack occurred within .the first year of service in 72 per cent; the

11. Bland, E. F.; White, P. D., and Jones, T. D.: The Development of Mitral Stenosis in Young People, Am. Heart J. **10**:995-1004 (Dec.) 1935.

incidence was highest in winter and spring months, and 36 per cent had experienced rheumatic fever prior to enlistment. Other factors, including geographic origin of the patient, density of population of the home location, physical hardships related to service and hereditary background, were either of no significance or completely overshadowed.

Infections of the respiratory tract, length of service and seasonal influences are closely interrelated and reflect the epidemiology of hemolytic streptococcus infections of the respiratory tract. The close relationship between such infections and rheumatic fever is well recognized.[10] The 78 per cent incidence in this series of infections generally attributed to or complicated by hemolytic streptococci closely coincides with the 80 per cent incidence found by Coburn [10c] in naval personnel. Jones and Mote [10b] obtained a history of antecedent sore throats or colds in 63 per cent of a civilian group suffering from first attacks. Furthermore, the 37 per cent with a negative history showed immunologic evidence of a recent infection in most instances. Therefore, even though no symptomatic evidence exists, most first attacks can be attributed to recent hemolytic streptococcic infections.

Under the exigencies of war, the first year of service represents a phase of service life in which large numbers of unseasoned recruits are received at primary and secondary training centers where indoctrination and detachment occasion a rapid turnover of personnel. Few persons have a natural or acquired permanent immunity to hemolytic streptococcus infections.[12] Under these conditions, the major environmental factors favoring a high incidence of streptococcic infections of the respiratory tract are satisfied; namely, susceptibility of the host, high rate of change of population, overcrowding, widespread activity of a respiratory virus and the presence of one or more strains of hemolytic streptococci endowed with high communicability.[10c] Streptococcic infections of the respiratory tract, including scarlet fever, have been a serious problem in unseasoned recruits.[13] Therefore, it is not surprising that 72 per cent of the recruits susceptible to streptococcic infection acquired first attacks or recrudescences of preenlistment infection in the first year of service. The concentration of instances of rheumatic fever in the 18 to 20 year old group does not reflect an unusual susceptibility of this age group to the disease but reflects rather the age composition of the men exposed to the epidemiologic hazards of the first year in service.

12. Coburn, A. F., and Pauli, R. H.: Interaction of Host and Bacterium in Development of Communicability by Streptococcus Haemolyticus, J. Exper. Med. **73**:551-570 (April) 1941.

13. The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, United States Navy Department, Bureau of Medicine and Surgery, 1944.

Although only 5 to 20 men per thousand in the service population group had rheumatic fever prior to enlistment, this small group contributed 36 per cent of the 158 cases observed in this series. Master [3] found the even higher incidence of 54 per cent in a group of 80 persons who had rheumatic fever prior to enlistment, while Wendkos and Noll [9] reported 31 per cent and Jones [14] found that one third of the patients at Newport, R. I., training station had had rheumatic fever in childhood. An incidence of 30 to 36 per cent probably represents a more accurate estimate than the 54 per cent rate reported by Master.

Sixty-seven per cent of those with an infection prior to enlistment had been free from clinically recognizable infection for a period of six to thirty years (table 4). The observations of Wilson,[15] Keith [16] and Boone and Levine [17] clearly indicate that only a small minority experience recurrences after puberty and after freedom from infection for more than five years in a civilian environment. Therefore, most of this group would have escaped recrudescences in civilian life. Yet under service epidemiologic hazards this group alone contributed 33, or 21 per cent, of the 158 cases.

The occurrence of 7 first attacks and 10 recrudescences in the tropics reflects certain exigencies of military life already touched on rather than the inherent rate for rheumatic fever in tropical areas. This is borne out by the fact that 14 of the 17 cases occurred in the Hawaiian area, where large numbers of new arrivals are constantly received from the United States and transshipped to other areas. Furthermore, primary training stations located in North Carolina, Louisiana and California, where climatic conditions are favorable, experienced a high weekly morbidity rate of over 20 cases expressed in annual admission rates per thousand strength during the winter of 1944. Thus, under the exigencies of war, climate alone will not eliminate the hazard of service rheumatic fever.

Only 18 per cent of the 158 cases of acute polyarticular arthritis developed in the tropics, while 75 per cent of the 12 cases characterized by nondisabling pains of the joints and valvular heart. disease began there. This would indicate that, as in civilian population groups,[6a]

14. Quoted by Master.[3]

15. Wilson, M. G.: The Natural History of Rheumatic Fever in the First Three Decades, J. Pediat. **10**:456-465 (April) 1937.

16. Keith, J. D.: Observations on Diagnosis and Treatment of Rheumatic Heart Disease, Practitioner **151**:38-42 (July) 1943.

17. Boone, J. A., and Levine, S. A.: The Prognosis in "Potential Rheumatic Heart Disease" and "Rheumatic Mitral Insufficiency," Am. J. M. Sc. **195**:764-770 (June) 1938.

a larger proportion of cases occurring in tropical areas will exhibit mild polyarthritis than those occurring in temperate zones, and the problem of accurate recognition is enhanced.

The 7 per cent incidence of significant residual cardiac damage in patients who were free from heart disease before the present attack is considerably lower than the incidence in children [18] but it coincides with the observations of DeLiee, Dodge and McEwen [19] concerning civilians 25 years of age or older. As already stated, most patients with active infection in this hospital were treated by the intensive salicylate regimen which Coburn [5] found prevented significant cardiac residua. Those who were free from clinically recognizable carditis when therapy was instituted in this hospital escaped residual damage, but residual stigmas were not prevented in patients who already exhibited significant carditis before treatment was begun. Since the treatment regimen before admission to this hospital is unknown in most instances, the possible influence of Coburn's intensive salicylate regimen on the data presented cannot be estimated.

Some of the patients who escaped with normal hearts, had clinical and/or electrocardiographic evidence of carditis during the active phase of infection. This regression of clinical and electrocardiographic signs of carditis is a common observation. Furthermore, this favorable sequence of events occurred in 8.3 per cent of 1,000 children and adolescents stigmatized with rheumatic heart disease who were observed over a ten year period by Bland, Jones and White.[18] Therefore, the possibility exists that further regression of physical signs may occur in the 7 per cent in this series classed as suffering permanent significant cardiac damage from this attack.

The outlook for the patients who were entirely free from residual evidence of heart disease or classed as having potential rheumatic heart disease can be considered favorable. Bland and Jones [20] found that characteristic signs of permanent valvular deformity, not present at the time of the original illness, developed in 25 per cent of 314 children observed over a ten year period. This so-called delayed appearance was clearly associated with coexisting signs of recurrent rheumatic fever in two thirds of the group, while in the remaining one third it occurred insidiously. Boone and Levine [17] found the outlook was much more

18. Bland, E. F.; Jones, T. D., and White, P. D.: Disappearance of the Physical Signs of Rheumatic Heart Disease, J. A. M. A. **107**:569-573 (Aug. 22) 1936.

19. DeLiee, E. F.; Dodge, K. G., and McEwen, C.: The Prognostic Significance of Age at Onset in Initial Attacks of Rheumatic Fever, Am. Heart J. **26**:681-684 (Nov.) 1943.

20. Bland, E. F., and Jones, T. D.: The Delayed Appearance of Heart Disease After Rheumatic Fever, J. A. M. A. **113**:1380-1383 (Oct. 7) 1939.

favorable in an intermediate age group, averaging 13.8 years of age and observed for 9.5 years; in only 4.8 per cent of 166 patients with a history of rheumatic fever or chorea but with either a normal heart or a systolic murmur of not more than grade 1 intensity did signs of valvular deformity subsequently develop.   Bland and Jones [20] have expressed the opinion that the considerable difference in the incidence of delayed heart disease in the two groups reflects the milder character of rheumatic fever in the second decade of life in contrast to the first.   Therefore, the 93 per cent of service patients who escape significant residual cardiac damage, many of whom are already in the third decade of life, should face minimal danger of delayed valvular heart disease in subsequent years in terms of a civilian environment.   *The prognosis under the increased epidemiologic hazards of continued service cannot be estimated.*

CONCLUSIONS

1. Polyarticular arthritis is the major rheumatic manifestation witnessed in service personnel and occurs in the acute form in 71 per cent and in some form in 79 per cent of the cases.   The incidence of carditis without articular manifestations is 4.6 per cent and of valvular heart disease is 16.6 per cent.   In most of the cases of the latter group the disease existed prior to enlistment and does not reflect service rheumatic fever.

2. Rheumatic fever noted during military service occurs in tropical and subtropical as well as in temperate zones.   A greater percentage of military personnel experience mild polyarthritic manifestation in tropical areas, complicating the problems of diagnosis.

3. Four major factors are involved in the occurrence of rheumatic fever in military personnel: (1) streptococcic infections of the respiratory tract; (2) length of service; (3) seasonal influences, and (4) antecedent rheumatic infection.   Infections of the respiratory tract, length of service and seasonal influences are closely interrelated and reflect the epidemiologic hazards of hemolytic streptococcus respiratory infections in the first year of service.

4. Although only 5 to 20 per thousand persons in the service population have suffered from rheumatic fever prior to enlistment, this small minority accounts for 30 to 36 per cent of rheumatic attacks during military training.

5. Significant residual cardiac damage which had not existed previously occurred in 7 per cent of 158 patients with acute polyarticular rheumatic fever.   Sixty-six per cent escaped with normal hearts. Twenty-five per cent showed residual slight or moderate systolic mitral murmurs transmitted to or beyond the anterior axillary line, and they were classed as having potential rheumatic heart disease.   It seems likely

that less than 5 per cent of the patients who escaped with normal hearts or were classed as having potential rheumatic heart disease face the prospect of delayed significant cardiac residua in a civilian environment, but the prognosis under the increased epidemiologic hazards of continued military service cannot be estimated.

6. Abnormal electrocardiograms were encountered in 26 per cent of the 113 patients observed during active infection. Only 24 per cent of this group showed residual physical signs of significant cardiac damage.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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THE material for this article has been selected from publications which have appeared from July 1944 to June 1945. In this review [1] especial emphasis is placed on subjects of particular current importance, e. g., biologic false positive reactions to serologic tests for syphilis and new methods of treatment, especially with penicillin, though articles on other important subjects are not neglected. The number of European journals available for review is negligible.

EXPERIMENTAL SYPHILIS

Chesney and Woods [2] report experiments to determine the extent to which a primary syphilitic infection of the cornea in rabbits is followed by the development of a local corneal immunity, by the generalized spread of Treponema pallidum and by the development of a general

1. (a) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1923. (b) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936; (c) **60**:887 (Nov.) 1937. (d) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **62**:1029 (Dec.) 1938. (e) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, ibid. **64**:1053 (Nov.) 1939. (f) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **66**:1112 (Nov.) 1940. (g) Mohr, C. F.; Padget, P.; Hahn, R., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **69**:470 (March) 1942. (h) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **70**:836 (Nov.) 1942; (i) **72**:635 (Nov.) 1943. (j) Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G., and Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **74**:390 (Nov.) 1944.

2. Chesney, A. M., and Woods, A. C.: Further Observations on the Relation of the Eye to Immunity in Experimental Syphilis: II. The Development of Immunity After Primary Intracorneal Inoculation, J. Exper. Med. **80**:357 (Nov.) 1944.

immunity to the infection. Female rabbits were inoculated intracorneally with a virulent strain of T. pallidum, and the disease was allowed to run its course, until the lesions which had developed at the site of inoculation had healed spontaneously. Popliteal lymph nodes transferred from about one half of these animals to normal male rabbits proved in almost every instance to contain virulent spirochetes, showing that generalization of the syphilitic infection is the rule after intracorneal inoculation. All animals were treated with arsphenamine after the local lesion had subsided. The rabbits were then reinoculated with the homologous strain of spirochetes, injections being made into the cornea originally inoculated and also into the skin of the back. In one experiment both corneas were reinoculated.

The incidence of lesions developing in either cornea after reinoculation was higher than the incidence of lesions developing in the skin. The lesions developing in the corneas of the "immune" animals had a longer period of incubation and were of shorter duration on the average than the lesions in the control group. Inoculation of the cornea of rabbits with T. pallidum is often followed by the development of immunity to the homologous strain of organisms. This immunity is imparted to the skin to a greater extent than to either the cornea inoculated originally or the opposite uninoculated cornea. It persists after treatment with arsphenamine. It appears to be more marked the longer treatment is postponed.

In another paper, Chesney and Woods [3] report further observations on the relation of the eye to immunity in experimental syphilis. Two experiments were conducted in which rabbits originally inoculated with syphilis and treated late in the course of the disease (one hundred and seventy-fourth to two hundred and tenth day) were reinoculated subsequently in both corneas with the homologous strain of spirochetes. In each animal one cornea had been previously inoculated with dead tubercle bacilli. This procedure was carried out in order to bring about a nonspecific inflammatory reaction with resultant vascularization, the intention being to determine whether vascularization would render the cornea more resistant to reinoculation with T. pallidum. The results of both experiments were inconclusive though similar.

While in the immune animals the behavior of the left corneas (into which dead tubercle bacilli had previously been injected) toward a second inoculation with a homologous strain of T. pallidum did not differ sharply from that of the right corneas, which had not been rendered

3. Chesney, A. M., and Woods, A. C.: Further Observations on the Relation of the Eye to Immunity in Experimental Syphilis: III. The Influence of a Non-Specific Inflammatory Reaction in the Cornea on the Development of Immunity in That Tissue After Intratesticular Inoculation, J. Exper. Med. **80**:369 (Nov.) 1944.

vascular by the injection of the bacilli, nevertheless the same trend was observed in each experiment. This trend was toward a greater resistance to a second inoculation with homologous syphilitic virus on the part of the vascularized left corneas. This might theoretically be due to one of two factors: (a) exposure of the corneal cells to a greater amount of antigen brought to them by the new vessels in the cornea, with a resultant active cellular response, or (b) the presence of an increased amount of circulating humoral antibodies.

Wile and Johnson [4] undertook experiments to determine the usefulness of white mice as carriers of syphilitic infection, and whether after inoculation T. pallidum survived in the spiral form or whether evidence could be found of a granular or infravisible form. They inoculated three groups of animals with the Nichols strain of T. pallidum. In one group they introduced the inoculum intraperitoneally, in the second group intracranially and in a third group intracutaneously, utilizing a previously produced marsupial pouch. Similar inoculations were carried out on splenectomized and on nonsplenectomized animals. After forty-eight to one hundred days the organs of the inoculated mice were ground up and injected into rabbit testes. In rabbits inoculated with organs from all three groups of mice typical testicular syphilomas developed. The infection was as readily conveyed from mouse tissue in splenectomized as in nonsplenectomized animals. Despite repeated efforts to demonstrate the spiral form of the organisms by dark field and tissue-staining technics, none was found in the mouse inoculums which resulted in infection in rabbits. Furthermore, no histologic changes suggestive of syphilis could be demonstrated in any of the mouse tissues examined. These facts led Wile and Johnson to believe, with certain earlier workers, that an infectious granular or infravisible form of the spirochete of syphilis does exist.

SERODIAGNOSIS OF SYPHILIS

Quantitative Serologic Tests.—Heyman [5] reemphasizes the value of quantitative serologic tests for syphilis in selected cases. With the aid of case reports, he points out the worth of serial determination of serum reagin in the diagnosis of primary syphilis when results of repeated dark field examinations are negative and discusses the detection of early congenital syphilis, the recognition of relapse in early syphilis following treatment, the differentiation of seroresistance from serologic

4. Wile, U. J., and Johnson, S. A. M.: The Use of Splenectomized and Non-splenectomized Mice in the Production of Experimental Syphilis in Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **28**:422 (July) 1944.

5. Heyman, A.: Quantitative Serologic Tests for Syphilis, New England J. Med. **232**:124 (Feb. 1) 1945.

relapse, the detection of the prozone phenomenon and the serologic follow-up of patients suspected of having biologic false positive reactions.

BIOLOGIC FALSE POSITIVE REACTIONS TO SEROLOGIC TESTS FOR SYPHILIS

Davis [6] has written a comprehensive article on the subject of biologic false positive reactions to serologic tests for syphilis with an exhaustive review of the literature. He summarizes as follows:

The serologic tests for syphilis are subject to marked variations in sensitivity; these largely account for the discrepancies in published reports on the incidence of biologic false positive tests in various diseases. Many of the cases reported have undoubtedly been technical false positives based on unreliable earlier Wassermann tests. Standards of performance of Wassermann (complement fixation) and flocculation tests have been elevated by international and United States Serologic Evaluation Surveys, but fluctuation in day to day results on weakly positive sera is still inevitable. In order to avoid technical false positive reactions, it is desirable to obtain more than one positive test before considering a case biologic false positive.

The incidence of transient positive tests following acute infections depends largely on the frequency of testing during the acute and convalescent stages. Although post-infectious or post-vaccinial positive reactions occasionally last as long as 3 months, most become negative within a few days or weeks. Since it is customary to perform serologic tests on hospital patients only on admission, at which time acute infections have not fully developed their antibodies, it is likely that the ability of many common infections to lead to false positive serologic tests is grossly underestimated. Those causes of transient positive reactions (malaria and vaccination) which have been tested at short intervals have shown some degree of reaction in nearly 100% of the cases, but the majority of these were only 1 or 2 plus reactions, and would ordinarily be reported as negative or doubtful. Similar studies would be desirable in a variety of common infectious diseases.

False positive serologic tests are common (more than 10% of cases) in leprosy, malaria in the acute stages, infectious mononucleosis, vaccination against smallpox, rat-bite fever due to Spirillum minus, relapsing fever, lupus erythematosus, and possibly certain types of atypical pneumonia. There is no reliable evidence that the serologic tests are significantly affected by pregnancy, menstruation, scarlet fever, jaundice (other than infectious), subacute bacterial endocarditis, tuberculosis, or hyperproteinemia, in spite of earlier reports. Inadequate data are available on measles, mumps, infectious hepatitis, lymphopathia venereum, chancroid, and many other diseases.

Transient false positive reactions may occur in apparently normal individuals without recent illness, and in cases of some diseases in which the incidence is so low as to suggest that the relationship may be coincidental. It has recently been suggested that even persistently positive reactions may occur in non-syphilitic patients. Since a large proportion of seropositive patients have no syphilitic lesions at autopsy, it is entirely possible that many seropositive persons without a history or signs of the disease have been mistakenly diagnosed and treated for latent syphilis. Surveys of normal populations have shown that the incidence of false

6. Davis, B. D.: Biologic False Positive Serologic Tests for Syphilis, Medicine **23**:359 (Dec.) 1944.

positive reactions is only a small fraction of 1%, but in large serologic dragnets the number of innocent victims may be large, and the psychological, social, and legal consequences to the individual may be serious.

Since low titer syphilitic sera may show discrepancies between the results obtained with various test antigens, and fluctuation in apparent reactivity of successive sera, these are not adequate criteria for considering a positive serum false. . . .

Some of the false positive reactions may be eliminated in the future by purification and improvement in specificity of lipid antigens of the Wassermann group, but there is no reason to expect all false Wassermann antibodies to differ in any given respect from the true antibody. Attempts to find consistent empirical physico-chemical differences between syphilitic and false positive sera have thus far failed. To the reviewer [Davis] the most promising approach to the problem is the detection of antibodies to antigens of the spirochete other than Wassermann antigen. Although virulent Treponema pallidum has not yet been cultivated, certain strains of cultured spirochetes have been found to be antigenically distinct from Wassermann antigen in the complement fixation test, and to detect syphilitic sera with encouraging regularity. The specificity of such a spirochetal antigen was found in the 1941 U. S. Serologic Evaluation Survey to be too low to permit its use as a serodiagnostic procedure, but this does not eliminate its potential value as a verification test. Further work is indicated.

. . . A positive serologic test is not an emergency. The most important procedure, in the absence of pregnancy, is a probationary period of at least 3 months before starting treatment. While many false positive tests will be revealed as transient during this period, there are no verification tests available today to help in the diagnosis of those which remain positive.

Fractionation of Serum Globulin.—Neurath and his associates [7] publish a preliminary communication concerning an important and extensive study directed toward the development of a serodiagnostic method for the differentiation between syphilitic serums and those which give biologic false positive reactions. They believe that in these two groups of serums the reactive antibodies differ from each other in certain significant respects. Serums from patients with syphilis differed noticeably from normal serums, exhibiting electrophoretically decreased albumin and increased gamma globulin contents. The difference is both relative and absolute. Serums with biologic false positive reactions from presumably normal persons showed differences from normal serums qualitatively similar to those of syphilitic serums but of considerably smaller magnitude. However, serums with biologic false positive reactions from persons known to have diseases other than syphilis gave electrophoretic results essentially like those obtained with syphilitic serums.

When the various components of the serum were separated by either of two alternative chemical methods of fractionation, it was found

7. Neurath, H.; Volkin, E.; Erickson, J. O.; Putnam, F. W.; Craig, H. W.; Cooper, G. R.; Sharp, D. G.; Taylor, A. R., and Beard, J. W.: The Serological Diagnosis of Syphilis, Science **101**:68 (Jan. 19) 1945.

that fractions G I and G II contained most of the serologic activity, whereas crude albumin was always serologically inactive. The sum total of the individual titers of the isolated fractions of the syphilitic serums was consistently less than that of whole serums, whereas with serums giving biologic false positive reactions elimination of crude albumin resulted in a significant increase in the titer of the globulins over that of the parent serums. This differential behavior, particularly pronounced with weakly reactive serums, suggested an inhibitory effect of crude albumin on the reaction of antibodies of serums having biologic false positive reactions with lipoidal antigen.

It was further found that addition of the crude albumin fraction to globulin fractions derived from serums with false positive reactions caused complete inhibition of specific flocculation with lipoidal antigen. as well as redispersion of floccules formed before crude albumin was added. This inhibitory phenomenon did not, however, occur when a test was made with globulins isolated from syphilitic serums. The inhibitor has not yet been isolated and identified, but work is in progress toward this end.

Neurath and his group have demonstrated that the antibodies of serums with false positive reactions are more susceptible to inactivation by heat than those of syphilitic serums. Finally, they have achieved a considerable degree of concentration of the syphilitic antibody by adsorption from whole serums on freshly precipitated calcium phosphate followed by precipitation of the eluate with ammonium sulfate. Their observations "indicate that the antibodies of truly syphilitic sera, reactive with lipoidal antigen, differ from those of biologic false positive sera in certain chemical and immunological respects. The possibility of the application of these findings to the development of a practical method of differentiation is being explored."

To the reviewers this work of Neurath and his associates seems the most promising present avenue of approach toward solution of the difficult problem of serologic recognition of biologic false positive reactions to serologic tests.

Cooper[8] reports the result of electrophoretic analysis of syphilitic serums under varying conditions. Two strongly seropositive serums from patients with clinical syphilis were studied. Inactivation by heating to 56 C. for thirty minutes produced no significant change in the distribution of the electrophoretic fraction. Flocculation with Kahn antigen resulted in a decrease in gamma globulin. This suggests that reagin is associated with this fraction. When electrophoretic analyses and serologic tests were performed on protein fractions obtained by

8. Cooper, J. A.: Identification of Serum Fraction Carrying Syphilitic Reagin by Electrophoresis, Proc. Soc. Exper. Biol. & Med. **57**:248 (Nov.) 1944.

salting out with ammonium sulfate, reagin appeared to be associated with the beta or gamma globulin fractions or with both.

In another experiment, Cooper[9] studied by electrophoresis serums from 13 patients with various types of syphilis. Although the total protein concentrations in these serums were within the normal range, there was characteristically a decrease in the albumin concentration and an increase in all three globulin fractions. According to Cooper, this change in the serum protein picture occurs soon after infection with syphilis and persists throughout the course of the disease in the absence of adequate treatment. There was no apparent correlation between the quantitative Kahn titer and the increase in concentration of the total globulin or of any electrophoretic fraction. Gamma globulin was the fraction with which syphilitic reagin appeared to be associated. In 5 patients suspected of having biologic false positive reactions the characteristic changes found in syphilis did not occur.

Kahn and McDermott[10] report that among 1,400 recently inducted Naval personnel 69 were found to have positive Kahn reactions of intensities ranging from doubtful to 4 plus. Sixty-seven of these positive reactions, studied by Kahn's "verification" technic, were biologic false positive results. It was later learned that the donors of these 67 blood specimens had been vaccinated against smallpox about two months previously. In follow-up Kahn tests of 45 of the 67 seropositive nonspecific reactors reactions became negative in all but 4, who later reverted to seronegativity after an interval of two months. These results indicate to the authors that false positive reactions are detectable by means of the Kahn "verification" test. It has not yet been shown, however, that Kahn's misnamed test can actually differentiate or "verify" the positive results obtained in syphilis and other conditions.

Escobar[11] concludes that the Kahn "verification" test is of no value in differentiating between pinta and syphilis.

Rein and Elsberg[12] provide a comprehensive discussion of "verification" tests in the serodiagnosis of syphilis and conclude that none of these methods so far devised, including that of Kahn, can distinguish consistently between true and false positive reactions. They suggest that any new "verification" test should be subjected to critical evalua-

9. Cooper, J. A.: An Electrophoretic Study of Syphilitic Sera, J. Invest. Dermat. **6**:109 (April) 1945.

10. Kahn, R. L., and McDermott, E. B.: The Verification Test in Post-Vaccination Cases, J. Bact. **47**:460 (May) 1944.

11. Escobar, J. J.: The Reaction of the Kahn Verification Test in Pinta, Bol. clín., Univ. de Antioquia **6**:543 (Nov.) 1940.

12. Rein, C. P., and Elsberg, E. S.: Are Current Verification Tests of Practical Value in the Serodiagnosis of Syphilis? J. Invest. Dermat. **6**:113 (April) 1945.

tion by a selected committee of serologists and clinicians before it is released for general clinical use.

Biologic False Positive Tests in Malaria.—Rosenberg[13] aimed to determine which of several serologic tests for syphilis gave the least proportion of falsely positive reactions in patients with malaria and whether it was possible to distinguish malaria from syphilis on the basis of definite patterns of positivity among the different tests. He found that cases of mixed infections (Plasmodium falciparum and Plasmodium vivax) gave the highest incidence of positive results with all tests. Plasmodium malariae infections were not included in this study. The "strongest positive" reactions were obtained between seven and ten days after the first chill and persisted for from four to six weeks. The serologic reactions tended to remain positive longer in case of infections with P. falciparum. When parasites persisted despite the lack of clinical evidence of malaria, the falsely positive reactions remained at a high level. Fever per se could not be correlated with positive reactions. A characteristic pattern of positivity was found in most malarial serums. Generally the Kahn and Mazzini flocculation tests elicited positive reactions, the Kolmer complement fixation positive or doubtful reactions, the Kline flocculation test doubtful or weakly positive reactions and the Eagle and Hinton flocculation tests negative reactions or reactions which if positive soon reverted to negative.

Potter and his co-authors[14] have attempted to discover the effects of malaria on the reaction to the Wassermann test of the spinal fluid. From 100 consecutive patients with malaria specimens of blood and spinal fluid were taken within forty-eight hours of their entrance into the hospital. With the exception of 1, all had infections with P. vivax. These 100 patients gave no history of syphilis, and none had previously had such a diagnosis. Those who had positive or doubtful reactions to blood tests had tests repeated about once a week until negative reactions were obtained. Twelve per cent had positive reactions to serologic tests of the blood and 10 per cent had doubtful reactions. All of the 100 patients had negative reactions to the Wassermann test of the spinal fluid. One spinal fluid contained 17 cells, of which 6 were polymorphonuclear and 11 were lymphocytes. The remainder of the specimens had 10 or less cells. In 3 cases the total protein was 75 mg. per hundred cubic centimeters. In the remainder it was 50 mg. or less per hundred cubic centimeters.

13. Rosenberg, A. A.: Effect of Malaria on Serologic Tests for Syphilis. Bull. U. S. Army M. Dept., January 1945, no. 84, p. 74.

14. Potter, H. W.; Bronstein, L. H., and Gruber, C. M.: Blood and Spinal Fluid Tests for Syphilis in Malarial Patients. J. A. M. A. **127**:699 (March 24) 1945.

Cox and Durant [15] discuss the influence of malaria on flocculation and complement fixation tests for syphilis. Both tests were made on 175 specimens of serum from nonsyphilitic patients with acute malaria and on 140 specimens of serum from nonsyphilitic convalescent malarial patients. Of the 175 specimens followed during the acute phase of malaria, 17 were reported as showing doubtful or positive reactions, whereas a larger number (22 out of 140) of specimens of serum from convalescent patients were reported as giving positive reactions. Neither this study nor any other so far published, however, clarifies the question of false positive reactions to serologic tests in chronic malaria.

Smallpox Vaccination.—A case of smallpox in the Philadelphia area led to the mass vaccination of approximately 1,000,000 persons. Because of this, Favorite [16] had the opportunity to study 202 vaccinated persons, mostly medical students and nurses. In 44 of these there developed a primary cutaneous (nonimmune) reaction at the site of inoculation; in 134 there developed a local accelerated (vaccinoid) form, and 24 were immune. Serologic tests of the blood for syphilis were performed on this group within a reasonably short time prior to vaccination. Of the 202 persons on whom a single blood test was made after vaccination, 19 were found to have positive reactions by one or more serologic technics. These were examined from ten to fifty-seven days following vaccination, but 93.6 per cent of the repeat tests were made before the forty-third day. Twenty-five persons who had negative reactions fourteen days after vaccination were examined fourteen days later, or approximately one month after vaccination. Four of this group were then found to have positive reactions. The incidence of false positive reactions for syphilis following vaccination was 11.8 per cent [sic] regardless of type of vaccination reaction. All the false serologic reactions occurred in the nonimmune and accelerated groups and none in the immune group. All persons with positive reactions to tests were reexamined at regular intervals. At the end of sixty days only 8 had positive reactions, while in eighty days 4 had weakly positive reactions; 2 patients continued to have positive reactions for one hundred days, and the reactions of all became negative within one hundred and twenty days.

Later the entire student body of a medical school was vaccinated against smallpox. Six months later, when a new freshman class had

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15. Cox, C. B., and Durant, M. J.: The Influence of Malaria on the Kline and Complement Fixation (Wassermann) Tests for Syphilis, M. J. Australia **1:** 320 (March 31) 1945.

16. Favorite, G. O.: Factors Influencing False Positive Serologic Reactions for Syphilis Due to Smallpox Vaccination (Vaccinia), Am. J. M. Sc. **208:**216 (Aug.) 1944.

enrolled, the entire group was revaccinated, this time not only against smallpox but also against typhoid, paratyphoid and tetanus. This procedure offered an opportunity to determine the role played by the latter type of vaccinations. This study of Favorite's included 323 persons, three fourths of whom had been vaccinated six months previously. Blood tests were made on all prior to revaccination. In 6 subjects a primary cutaneous reaction developed and in 71 an accelerated form; 246 were immune. One month after revaccination, repeated serologic tests for syphilis were performed. Reactions previously seronegative were now positive in 15 persons, among whom 5 had had accelerated and 6 immune vaccinial reactions. Of all these immune subjects, in 2.4 per cent positive serologic reactions developed.

Infections of the Upper Respiratory Tract.—Miscellaneous Immunizations: During the early winter of 1943 there was a moderately severe epidemic of infections of the upper respiratory tract at Fort Jackson, S. C., occurring for the most part in troops who had recently received routine Army immunizations. Loveman [17] reports that when a false positive serologic reaction was suspected in any of these patients, a quantitative serologic test for syphilis was made and repeated as frequently as every week or two until a decision was reached as to biologic false positivity. All were followed for at least one month and often for as long as six months. One hundred soldiers were suspected of having false positive serologic reactions for syphilis. All had at least two initial positive serologic reactions and from two to twenty reactions during their follow-up period. The average time from the first immunization to the appearance of the first positive serologic reaction was thirty-two days. The greatest number of days was one hundred and twenty, and the shortest, five. Ninety-seven per cent stated that they had not had previous penile lesions, and only 4 per cent gave a history of having had gonorrhea. Eighty-six per cent had had both a recent infection in the upper respiratory tract and recent immunizations. Although it was impossible to determine which of these factors was responsible for the false positive serologic reaction, Loveman felt that the latter played a more important role than did the former.

Some supposedly false positive reactions remained for as long as six months. A quantitative test was of definite value in differentiating true from false positive types of reactions. A gradual decrease in titer without specific therapy practically always presaged an eventual negative reaction and thus indicated a false positive reaction.

17. Loveman, A. B.: False Positive Serologic Reactions for Syphilis: Report of One Hundred Cases Following Routine Immunizations and Upper Respiratory Infections, Bull. U. S. Army M. Dept., September, 1944, no. 80, p. 95.

Miscellaneous Conditions.—Rein and Elsberg [18] have studied the serums of persons with the following infections:

1. Vaccinia: Serum was obtained at weekly intervals from 129 patients after smallpox vaccination, in 80 of whom vaccinia developed; 49 had vaccinoid reactions. Of those with vaccinia, 52.2 per cent showed false positive reactions to blood tests; of those with vaccinoid reactions, 34.7 per cent; and of the total, 44.9 per cent. The majority (86.2 per cent) showed the first positive reaction to a blood test between the eighth and the fourteenth day after vaccination, though in some this was delayed to as late as the twenty-first day. Rein and Elsberg were unable to correlate the severity of the response to the vaccination with the height of the quantitatively titered reaction to the serologic test.

In a small series of patients studied serologically after combined typhoid and tetanus immunization the incidence of false positive reactions was insignificant.

2. Infections of the Upper Respiratory Tract: Of 72 patients with primary atypical pneumonia followed for brief periods, many with only one serologic examination, 23.6 per cent had positive serologic reactions. False positive reactions were also observed in 20.2 per cent of 79 patients with miscellaneous infections of the upper respiratory tract.

3. Leprosy: Eighty-five per cent of 80 presumably nonsyphilitic lepers had positive reactions to serologic tests for syphilis.

4. Filariasis: Six (11.3 per cent) of 53 specimens gave doubtful or positive serologic reactions.

5. Leptospirosis: Of single specimens from 87 patients with Weil's disease 43.6 per cent had positive reactions.

6. Malaria: In 44.4 per cent of a small series of nonsyphilitic seronegative inoculated persons false positive reactions developed.

7. Typhus: Single specimens were taken from 104 patients with epidemic and murine typhus, and 39.4 per cent gave positive reactions to serologic tests for syphilis.

The suggested method of study of patients with presumed false positive reactions includes a detailed history, a complete physical examination, a roentgenologic study of the heart and aorta, an examination of the spinal fluid, an examination of contacts and repeated quantitative serologic tests for syphilis for a minimum of three months.

In a later paper, Rein and Elsberg [19] analyze in more detail the

18. Rein, C. R., and Elsberg, E. S.: False Positive Serologic Reactions for Syphilis with Special Reference to Those Due to Smallpox Vaccinations (Vaccinia), Am. J. Syph., Gonor. & Ven. Dis. **29**:303 (May) 1945.

19. Rein, C. R., and Elsberg, E. S.: Studies on the Incidence and Nature of False Positive Serologic Reactions for Syphilis, Am. J. Clin. Path. **14**:461 (Sept.) 1944.

serologic results obtained in the 129 patients vaccinated for smallpox referred to briefly earlier.

Biologic False Positive Reactions to Wassermann Tests of Spinal Fluid.—Scott, Reynolds and Mohr [20] report 7 instances of biologic false positive reactions to Wassermann tests of spinal fluid in seronegative (blood) nonsyphilitic persons during the course of meningitis and 1 instance in which transfer of reagin from blood to spinal fluid may have occurred. The meningitis was tuberculous in 3 patients, meningococcic in 2 and aseptic lymphocytic in 2. In all patients the positive reaction to the Wassermann test of the spinal fluid was confirmed by one or more repeat tests. In all the cases reported the false positive reactions in the spinal fluid were of short duration, but in 1 patient with chronic lymphocytic meningitis the spinal fluid was repeatedly positive during the first forty days of the illness, reverted spontaneously to negative, positive again one hundred and sixteen days after the onset of the disease, at which time the patient suffered a relapse of meningitis, and again reverted spontaneously to negative. Unconfirmed positive reactions to Wassermann tests of the spinal fluid were observed in 1 patient with meningitis due to infection with alpha hemolytic streptococcus, in 2 with meningitis due to infection with Staphylococcus aureus, in 1 with poliomyelitis and in 4 with subarachnoid hemorrhage. The authors conclude that the diagnosis of neurosyphilis based on a positive reaction to a Wassermann test of the spinal fluid alone is unjustified for patients suffering from meningitis and other acute intracranial disorders until repeated examination, performed after these processes have subsided, demonstrate the continued presence of reagin.

VENEREAL DISEASE AND THE WAR

The surrender of the Axis powers and the rapid demobilization of the armed forces abruptly lessen the interest of the general reader in the more purely military aspects of the venereal diseases. Many of the papers which have appeared within the past year are therefore purposely omitted from this review; others are briefly mentioned because of some particular interest.

In the latter category, since it deals with venereal diseases in aviation personnel and is therefore of interest to physicians concerned with civilian as well as with military flying, is the article by Dyar and Scholtz.[21]

20. Scott, V.; Reynolds, F. W., and Mohr, C. F.: Biologic False Positive Spinal Fluid Wassermann Reactions Associated with Meningitis: Report of Eight Cases, Am. J. Syph., Gonor. & Ven. Dis. **28**:431 (July) 1944.

21. Dyar, R., and Scholtz, J. R.: Venereal Disease and Flying Personnel, J. Indiana M. A. **37**:435 (Sept.) 1944.

Physical standards of flying personnel are extremely high, and reactions to drugs may be the cause of accidents; concealed infection and treatment unknown to medical officers take on an added significance when aviators are involved. Expressed in terms of physical and physiologic abilities, the qualities which the flyer must have are a high level of consciousness, alertness, orientation, judgment of time and distance, muscular coordination, short reaction time, visual efficiency, tolerance of altitude and ability to withstand fatigue. Any factor which adversely affects these qualities impairs the ability of the individual to perform flying duty. Venereal diseases must be considered from three standpoints as they affect flying performance—namely, the possible effects of the disease on normal physiology and on the occurrence of disturbances characteristic of flight and the possible accentuation of minor pathologic changes, ordinarily below the clinical horizon, under flying conditions.

Lymphogranuloma venereum and granuloma inguinale are disqualifying for any type of military service. These diseases are chronic; no satisfactory treatment is available, and they represent a medical burden even though in most instances they do not result in serious physical disability. Persons having uncomplicated infections with Ducrey's bacillus are acceptable for general military service, since the great majority of them readily respond to sulfonamide drugs and are cured within a few weeks. Such persons are then perfectly able to carry on any type of military duty, including flying, if otherwise qualified.

Persons infected with uncomplicated gonorrhea are also acceptable for general military service, since it, too, can in most instances be rapidly cured, after which the patient is physically qualified for any type of military duty. If he is receiving sulfonamide drugs, the patient is temporarily disqualified for flying. The availability of penicillin reduces the period of disability from gonorrhea almost to the vanishing point, since a curative dose can be administered in less than twelve hours and there are no reactions to the drug which prevent immediate return to flying duty.

The presence of syphilis of the central nervous or cardiovascular systems, or of the viscera or, in fact, any clinically active syphilis—other than primary and secondary—is disqualifying for flying duty in the Army. On the other hand, persons with primary, secondary or latent syphilis, regardless of the amount of treatment, are so qualified when not actually under treatment.

Most of the discussion by Dyar and Scholtz of drugs for flying personnel is outmoded by the advent of penicillin, which has almost completely changed the perspective in regard to both gonorrhea and syphilis. This drug is so completely free of untoward reactions that

flying personnel may return to flying duty immediately on completion of treatment.

There are no verified reports of air accidents which can be attributed to the effects of venereal diseases or of the drugs used in their treatment. Several such reports have been investigated, and in no instance has the disease or the drug been proved to have been the proximate cause of the accident. However, the nature of air accidents is such that it is usually impossible to determine what role, if any, medical factors play.

Dyar[22] says that education, an important factor in the control of venereal diseases in civilian life, is the most significant part of the program in the Army. In civil communities sound efforts toward control are based primarily on epidemiology, and the responsibility for control of the sources of venereal disease infection is shared jointly by civil health agencies and law enforcement agencies. The importance of education concerning venereal disease is officially recognized in the United States Army by regulation and directive. The fact that most of the current infections occur in personnel who are ignorant of the facts regarding venereal disease indicates either that there has been a failure to appreciate the importance of education, or that there has been neglect of utilizing available technics and of developing new procedures.

Dyar emphasizes that education concerning venereal disease must be specially adapted to varying personnel; a few scientifically accurate facts must be presented with a fully defined purpose, and the presentation must be well organized, coordinated, progressive and repetitive, but at the same time simple, brief and attractive.

In a paper read before the National Venereal Disease Control Conference, Padget[23] says:

The venereal diseases will be, as they have always been, a world problem, and with the conditions which we may anticipate to obtain in a postwar world, with tremendous shiftings of large population groups and with travel between and intercourse among the various peoples of the world on a scale so far unprecedented, we may take for granted that the venereal disease problem will be international, and we in the United States may base our plans upon that concept. . . . Among the large body of men who eventually will return to the United States from Europe there will be a number who have acquired a venereal disease. This fact and its possible significance to the public health of the United States must be carefully considered. . . .

The venereal disease control program in the European Theater of Operations . . . got under way in the summer of 1942, and became a full-time venture in September

22. Dyar, R.: The Medical Officer and the Venereal Disease Education of the Soldier, Ven. Dis. Inform. **26**:27 (Feb.) 1945.

23. Padget, P.: U. S. Army Experiences in Venereal Disease Control in the European Theater of Operations, Am. J. Syph., Gonor. & Ven. Dis. **29**:352 (May) 1945.

of that year. . . . From the beginning it was apparent that whereas any venereal disease control program is made up of the same five or six basic ingredients, the technique of application of these various elements must be adjusted to meet local conditions. . . .

Basically, a venereal disease control program deals with four elements: the susceptible population—in our special case the soldier in the United States Army; the infected population—made up of the group of promiscuous women, an unknown number of whom are infectious at a given moment; the number of sexual contacts which take place between the susceptible group and the potentially infectious; and protective measures taken to reduce the risk of infection when exposure has occurred. . . .

As we review these various avenues of approach, examination of what is meant by education will suffice to illustrate the necessity for developing a venereal disease control program with consideration of local problems. All too frequently we encounter the use of the term "education" without the slightest consideration of what it is that should be taught. Certainly the soldier should know the fundamentals of human anatomy, sex hygiene and the nature of the venereal diseases. . . .

Our experiences with prophylaxis are most interesting. There was, of course, a considerable variation in education and training of the soldiers reaching us, depending on how long they had been in the Army before being shipped overseas. . . . In the United Kingdom, however, our soldiers encountered relatively few professional prostitutes. . . . The vast majority of the sexual intercourse which took place was on a friendly and noncommercial basis. This had the immediate and readily discernible effect of markedly reducing the impetus to seek station prophylaxis. . . . By contrast condoms were extensively used and chemical pocket prophylactic kits were not infrequently employed.

The situation in France has been entirely different. The soldiers are all aware that professional prostitution flourishes and up to the present there has been a much more extensive use of station prophylaxis than was the case in the United Kingdom. . . .

Surveying the situation, it became apparent that a contact investigation scheme was essential as a venereal disease control measure among our troops. The enactment of the British Defense Regulation 33B made it possible for us to obtain and transmit the necessary information concerning sex contacts, and the Chief Medical Officer of the Ministry of Health, Sir Wilson Jameson, gave our tentative plan enthusiastic approval and paved the way for arrangement with local Medical Officers of Health in the areas in which we had troops stationed. Eight U. S. Army nurses (regular members of the Army Nurse Corps) were selected as the field workers for the scheme by virtue of previous training and experience in public health nursing. . . . They interviewed soldiers with venereal disease, got from them as much as could be obtained regarding the identity of their sexual contact or contacts, identified such of these women as was possible and presented them with a tactfully worded invitation to avail themselves of the services of the nearest clinic of the local health authority. . . .

In the summer of 1942, when our first troop concentration in the United Kingdom began, the venereal disease rate among our troops in the United Kingdom was essentially the same as that obtained for troops in training in the United States. During the autumn and particularly in the general slump which followed the setting off of the African expedition, the venereal disease rates rose to reach a peak just after the turn of the year, at which time the rate was conspicuously higher than that obtained in the United States. Since that time, however, the rate has pro-

gressively declined, at first rapidly, in the first six months of 1944 more slowly, but the downward trend up until D Day was consistent and sustained, to compare favorably . . . with rates for the troops remaining in the United States.

In England, we had been the guests of people who spoke a similar and frequently understandable language and from whom we differed in morals and social customs only in details. In France, we encountered an equally friendly nation—a nation in fact more given to being demonstrative about friendship than are the British—but with a language which is strange to most of our soldiers, and manners and social customs which differ sometimes widely from our own. The differences are so great that in developing a venereal disease control program applicable to our troops in France, very little of our British experience could be employed. . . . All over France there are licensed brothels. Streetwalkers are also licensed. . . .

During the occupation in all communities in which we had troops garrisoned, the enemy had taken over one or more of the local brothels and had operated them exclusively for the Wehrmacht. Among captured enemy documents, we found what would be called in our Army an SOP (i. e., Standard Operating Procedure) for the creation and operation of brothels. This 17-page mimeographed circular is a masterpiece of completeness. . . . There was an elaborate procedure for gaining entrance. . . . In spite of this complicated ritual, the enemy had a disastrous time with venereal infections in his French garrison and in two areas in which we have captured complete records of the experience, the venereal disease rates were over 125 per 1000 per year. . . .

To complete the contrast is the situation with regard to the practicability of epidemiologic investigation. In the British experience . . . we could get information worth following for epidemiologic study. . . . In France, however, only a negligible number of our soldiers who acquire a venereal disease are able to give useful information regarding the identity of their contact. . . .

Schwartz [24] presents a current appraisal of the venereal disease situation in the United States Navy and suggests the trend of the future. Although the venereal disease rate for the entire Navy has fallen off sharply during recent years, and is now at the lowest point in the history of the Navy, roughly 25 new admissions per thousand men per year, the rate in the forces in the continental United States has been climbing steadily and at an increasing speed since 1942. The rate for 1943 was 9 per cent above that for 1942, and for the first six months of 1944, 11 per cent above that for 1943. The author points out that the general downward direction of the entire rate for the Navy reflects the very low rate now being experienced among substantial elements of the naval forces overseas and that this is a condition which normally accompanies intense combat activity. As combat activity decreases, a situation analogous to the experience after Armistice Day of World War I may well develop. At that time the rate increased within one year by 60 per cent. The author warns against complacency and reiterates the

24. Schwartz, W. H.: Venereal Disease Control in the Navy: A Current Appraisal with a Comparative Look at History and the Future, J. Social Hyg. **31**:34 (Jan.) 1945.

need for an intensified and expanded program for the control of venereal disease.

The author of a special article [25] finds that the average length of hospitalization for Army patients with venereal disease in 1939 was forty-two days. By 1944 this figure had declined to six and one-half days. Even in the face of a rise in admission rate, a saving in man power has been accomplished. The replacement of local therapy by sulfonamide drugs and of the latter by penicillin has effected as of September 1944 a tremendous decrease in the duration and complications of gonorrhea. For syphilis, the introduction in July 1942 of a twenty-six week plan of oxophenarsine hydrochloride–bismuth therapy effected a substantial saving in length of treatment. As of October 1944, War Department Technical Bulletin, TB Med. 106, "Penicillin Treatment of Syphilis,[26] introduced the treatment of syphilis with penicillin on an Army-wide basis. With a total dosage of 2,400,000 units given in sixty consecutive intramuscular injections at three hour intervals, day and night, the total treatment time for syphilis was reduced to seven and one-half days. This method is said to be at least as effective as any plan of treatment heretofore employed and much less dangerous.

Hinrichsen [27] discusses at length and in detail venereal disease in the major armies and navies of the world. Little actual statistical information was available before the nineteenth century. The articles does not lend itself to adequate abstraction, and the interested reader is referred to the original.

Civilian Aspects.—The author [28] of an editorial expresses doubt that, despite the promise of the new chemotherapeutic agents effective against syphilis and gonorrhea, the eradication or even the control of venereal disease is possible in the immediate future. Although the present low rate of these diseases in the armed forces is commendable, it is pointed out that it was not until after the last Great War that the incidence of syphilis and gonorrhea reached its peak. The recent advances in therapy, although highly effective, have introduced new problems for the health administrator—e. g., asymptomatic carriers of gonococci and an increased susceptibility to reinfection of patients with early syphilis

25. Improvements in Treatment of Venereal Disease, Bull. U. S. Army M. Dept., June 1945, no. 89, p. 76.

26. Penicillin Treatment of Syphilis, United States War Department, Technical Bulletin (TB Med 106), Washington, D. C., Government Printing Office, October 1944.

27. Hinrichsen, J.: Venereal Disease in the Major Armies and Navies of the World, Am. J. Syph., Gonor. & Ven. Dis. **29**:80 (Jan.) 1945.

28. Shall We Control Venereal Disease? editorial, Am. J. Pub. Health **34**: 1185 (Nov.) 1944.

treated by intensive methods. The need for more vigorous epidemiologic control is stressed.

Case Finding.—Heller [29] discusses future aspects of venereal disease control. He estimates that of about 230,000 new cases of syphilis contracted in this country annually, only about three fourths are discovered and treated and that less than one half of the patients found remain under treatment long enough to insure against infectious relapse. The unfound and untreated one fourth and the insufficiently treated lapsed cases are the source of infection for the annually recurring new crop of early syphilis, and they accumulate year in and year out to form the great reservoir of late and latent syphilis. No matter how effective new procedures of treatment may be, they can have little value for reduction of the rate of attack unless persons who are infectious are brought to the physician before they have spread their infections to others.

In the past, the English have not utilized the important case-finding and control measure—investigation of contacts—because the authorities considered this method to be an infringement of individual rights. Following the successful demonstration by a small team of United States Army Public Health Nurses in tracing the female contacts of personnel of the American armed forces in England, there has been in that country an awakening of interest in the investigation of contacts. Evidence of this is indicated by a series of articles [30] in the *British Journal of Venereal Diseases*. A pilot study instituted in Tyneside, a report of which is included in one of the papers, proved highly successful. The favorable comment evoked by the results of this experiment suggests a wide application of investigation of contacts in England in the future.

Sternberg and Larimore [31] believe that the postwar period will present far greater assets for the control of the venereal diseases than have been available at any previous time. A large number of physicians and lay personnel trained by the Army and experienced in the principles

29. Heller, J. R.: Venereal Disease Control of Tomorrow, J. Social Hyg. **31**:16 (Jan.) 1945.

30. (*a*) Manchee, D. M.: The Social Aspect of the Venereal Diseases: I. The Work of the Almoner, Brit. J. Ven. Dis. **21**:12 (March) 1945. (*b*) Walies, M. A.: The Social Aspect of the Venereal Diseases: II. Contact Tracing and the Prostitute, ibid. **21**:15 (March) 1945. (*c*) Johns, H. M.: The Social Aspect of the Venereal Diseases: III. Contact Tracing, ibid. **21**:17 (March) 1945; (*d*) The Social Background of Venereal Disease: A Report on an Experiment in Contact Tracing and the Prostitute and an Investigation into Social Conditions; Tyneside Experimental Scheme in Venereal Disease Control, October 1943 to March 1944, ibid. **21**:26 (March) 1945. (*e*) The Venereal Disease Contact, editorial, ibid. **21**:1 (March) 1945.

31. Sternberg, T. H., and Larimore, J. W.: Army Contributions to Postwar Venereal Disease Control Planning, J. A. M. A. **127**:209 (Jan. 27) 1945.

of venereal disease control will be available. The postwar population will be diluted by 9,000,000 soldiers, and thus the general educational level concerning venereal diseases will be raised to a new high; it seems certain that future programs for the control of venereal diseases will be accorded increased public support. Efforts to reimpose a black-out on the venereal diseases are doomed to failure. Remarkable advances in treatment climaxed by the introduction of penicillin will add great impetus toward achieving the goal of universal case finding and case holding. These factors, added to the stabilization of community life and the return of an opportunity to follow the natural instincts of monogamous relationships, all lead to the conclusion that there will be an unprecedented opportunity to reduce the incidence of the venereal diseases to a manageable minimum.

Ingraham and Greenbaum [32] point out a fundamental fact too often entirely ignored by venereal disease bureaus in health departments. The management of gonorrhea and syphilis in clinics reaches only a small portion of the persons infected. As the magnitude of the case-finding problem is more clearly defined and as the vast amount of hidden venereal disease, unknown to any source of treatment, becomes evident, the necessity of actively enlisting the support of the private physician becomes apparent. The Philadelphia Department of Public Health has utilized professional and lay education and adopted consultation and laboratory services together with distribution of free drugs. The interesting and unique factor in the Philadelphia program, however, is the active solicitation of the private physician by the health department, so as to integrate all available medical facilities toward the same end. It was found completely unsatisfactory merely to tell the prospective patient to consult his family physician. A direct appeal was made by a letter jointly sponsored by the County Medical Society and the Department of Public Health. Approximately two thousand, five hundred physicians responded, and three fourths of those who treated gonorrhea or syphilis (one thousand, one hundred and sixty-four physicians in all) agreed to have their names published for purposes of facilitating a proper patient referral mechanism in the community. A survey conducted to ascertain the effectiveness of this effort showed a definite increase in the number of patients with venereal disease receiving private medical care in Philadelphia. The prevalence of treatment for syphilis by private physicians has increased 86 per cent since 1940, and for gonorrhea 30 per cent in the same period.

32. Ingraham, N. R., Jr., and Greenbaum, S. S.: Public Health Venereal Disease Control: The Private Physician's Increasing Responsibility; a Report of the Success of Philadelphia's Cooperative Plan, J. A. M. A. **125**:527 (June 24) 1944.

DRUGS

Although the advent of penicillin in the treatment of syphilis has lessened interest in the toxic drugs arsenic and bismuth, there is, nevertheless, a strong possibility that both of the latter will continue to be of value for some years to come. It may be desirable to employ one or both of them simultaneously with penicillin or to use them alone, without penicillin, for certain special purposes. For these reasons it is still justifiable to devote considerable space to articles dealing with recent results obtained with these metals.

Oxophenarsine Hydrochloride.—Since it is frequently necessary to administer treatment for syphilis and gonorrhea simultaneously, Cranston, Clark and Strakosch [33] have studied the acute toxicity for mice of oxophenarsine hydrochloride and sodium sulfathiazole, given separately and together, in order to determine whether these drugs are synergistic, additive, antagonistic or without effect on one another as regards toxicity. By use of large numbers of mice and by administration of the drugs intraperitoneally, it was found that the combined toxicity was greater than that of either drug alone, as the LD_{50} dose of the combination was 65 per cent of the LD_{50} dose of each drug alone. The results indicated that the toxic effects are additive but less than algebraic summation.

Since the therapeutic efficacy of oxophenarsine hydrochloride in the treatment of experimental syphilis in rabbits is increased approximately fourfold when the drug is administered concurrently with physically induced fever while the toxicity is only doubled, Stokinger, Dorn, Boak and Carpenter [34] have studied the arsenic content of rabbit tissues following treatment with oxophenarsine hydrochloride and fever and with oxophenarsine hydrochloride alone, in an effort to determine whether a relationship exists between the distribution of arsenic and the increased therapeutic efficacy and toxicity. Significantly higher concentrations of arsenic were observed in the tissues of rabbits treated with oxophenarsine hydrochloride plus fever than in those treated with the drug alone. It was found that the elimination of arsenic was retarded in the fever-treated animals and that the greatest increase in arsenic content occurred in the liver and kidneys.

33. Cranston, E. M.; Clark, W. G., and Strakosch, E. A.: The Acute Toxicity for Mice of "Mapharsen" and Sodium Sulfathiazole Administered Separately and in Combination. J. Pharmacol. & Exper. Therap. **81**:284 (July) 1944.

34. Stokinger, H. E.; Dorn, F. L.; Boak, R. A., and Carpenter, C. M.: The Effect of Fever on the Distribution of Arsenic in the Tissues of Rabbits Injected Intravenously with Mapharsen, Am. J. Syph., Gonor. & Ven. Dis. **28**:465 (July) 1944.

New Phenylarsenoxides.—Continued efforts are being made to discover new arsenicals which have both a higher therapeutic index and lower toxicity. Eagle and his co-workers[35] have studied 13 amide-substituted phenylarsenoxides (-RCONH$_2$, -RSO$_2$NH$_2$) and found that they were, per unit of arsenic, only *4.5 to 13.5 per cent as toxic as the* parent phenylarsenoxide. The treponemicidal activity in vitro was not reduced to the same degree; therefore the ratio of treponemicidal activity to toxicity was 1.9 to 6.1 times more favorable than that of phenylarsenoxide. The favorable effect of amide groups was confirmed for ten of these compounds by assays of toxicity and therapeutic activity in syphilitic rabbits. The regularity with which substituents containing terminal amide groups decreased the toxicity and increased the chemotherapeutic index of phenylarsenoxide suggests that some members of this series may be of clinical utility.

Local Prophylaxis of Syphilis with Arsphenamine.—Eagle and his co-workers[36] have studied local chemical prophylaxis with phenylarsenoxides in experimental syphilis. They summarize as follows:

1. Nine trivalent arsenicals [all phenylarsenoxides] . . . have been studied with respect to prophylactic activity in rabbit syphilis. One-half c.c. of solutions in propylene glycol was rubbed for four minutes over a superficial skin incision, at varying intervals before and after its inoculation with a suspension of T. pallidum (Nichols' strain) containing 10[7] organisms per c.c.

2. All the compounds were found to be effective, and approximately in proportion to their direct treponemicidal activity. The concentration necessary to protect half the animals when applied four hours after inoculation varied from 0.06 to 0.15 per cent in the case of the more active compounds, to 1.5 per cent in the case of the least active compound.

3. The effective concentration of the p-CONH$_2$ phenyl arsenoxide varied with the time interval between inoculation and application. A 1:2,000 solution protected half the animals when applied five minutes after exposure; it required a 1:500 concentration to protect half the animals four hours after exposure; and only concentrations in excess of 1:100 had a similar effect 22 hours after exposure. The prophylactic efficacy of this compound, although definite, was somewhat less pronounced when it was applied before inoculation. The concentrations which protected 50 per cent of the animals when applied 5 minutes, 4 hours and 22 hours before inoculation were respectively, 1:2,000, 1:200-1:500, and 1:50.

4. The effect of the p-CONH$_2$ compound, and presumably, of the other arsenoxides here tested, was due to a direct treponemicidal action on the organisms in the skin itself, and not to a systemic effect on an established infection.

35. Eagle, H.; Hogan, R. B.; Doak, G. O., and Steinman, H. G.: The Toxicity and Treponemicidal Activity of Amide-Substituted Phenyl Arsenoxides and Their Derivatives, J. Pharmacol. & Exper. Therap. **81**:142 (June) 1944.

36. Eagle, H.; Hogan, R. B., and Fleischman, R.: The Local Chemical Prophylaxis of Experimental Syphilis with Phenyl Arsenoxides, Am. J. Syph., Gonor. & Ven. Dis. **28**:661 (Nov.) 1944.

(a) As shown by urinary and fecal excretion, of the 0.5 mg. which was regularly protective on local application 1 hour after inoculation, less than 10 per cent was absorbed through the skin. In rabbits averaging 2.5 kg., it required more than fifty times that amount of mapharsen injected intravenously to abort syphilitic infection when the animals were inoculated intratesticularly 1 hour previously with only 1,000 organisms.

(b) Even 100 times the concentration which was effective when applied over the inoculated area was ineffective when applied over a similar incision on the opposite side of the back, or 1 to 2 inches from the inoculated area.

5. It follows that, when a heavy suspension of T. pallidum is rubbed into an open cut in the rabbit skin, the organisms remain in the skin or adjacent soft tissues, susceptible to the local treponemicidal action of prophylactic agents, for as long as 8 to 22 hours.

6. The concentrations of arsenical effective for periods of four to eight hours after inoculation caused only slight reaction on intracutaneous injection.

7. The stability of the selected compounds here discussed, the time interval over which they remain effective, the low concentrations necessary within reasonable time periods, and the absence of local irritative effects at those concentrations, all offer promise that some of these compounds may be of value in the prophylaxis of the human disease.

Bismuth.—Kendell and his co-workers [37] present figures to demonstrate that after 2 cc. of oil-insoluble bismuth (150 mg. of elemental bismuth) administered sixteen hours before fever-chemotherapy treatment, the daily urinary excretion of bismuth during the first six days after treatment remains consistently lower than 2 mg. of elemental bismuth, the "therapeutic bismuth level." It was therefore decided to administer concomitant water-soluble bismuth (sodium bismuth thioglycollate) to a series of 69 patients. From the data presented it is evident that the addition of water-soluble bismuth to the described method of fever plus chemotherapy will raise the urinary excretion of bismuth to "the therapeutic level." However, the amount needed to attain this level cannot be given without potentially serious reactions. Of the 69 patients who received water-soluble bismuth in addition to oil-soluble bismuth, 10 had significant complications, and of these 3 were critically ill. There was 1 death from acute nephrosis and ulcerative stomatitis. During the period in which these 69 patients were studied, 173 other patients were given the same routine except for the water-soluble bismuth. Of these, 3 had complications and none was seriously ill. The complications in both series occurred during the postfever period and were classified as acute nephrosis, acute hepatitis, or azotemia and/or ulcerative stomatitis. The authors do not provide further clinical details concerning reactions to treatment.

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37. Kendell, H. W.; Craig, R. M.; Schwemlein, G. X., and Aron, H. C. S.: Artificial Fever-Chemotherapy: I. Bismuth Excretion Studies, Arch. Phys. Therapy **25**:593 (Oct.) 1944.

REACTIONS TO TREATMENT

Hepatitis.—The epidemic of jaundice in England during or after the administration of organic arsenicals has recently been shown to be infectious hepatitis of virus causation transmitted from patient to patient by technical error.[38]   This fact renders of secondary importance the papers of Peters and his associates [39] and Beattie and Marshall.[40] Before the demonstration of the virus origin of this epidemic of jaundice these investigators were engaged in a study of dietary deficiency as an etiologic factor and of certain forms of dietary treatment.   Peters and his group studied the prophylactic and curative effect (on jaundice) of cysteine, casein and methionine but without dramatically conclusive results.   Beattie and Marshall attempted to demonstrate that jaundice could be prevented by the administration of sulfur-containing amino acids (casein digest, cysteine, methionine) during antisyphilitic treatment, but again without definite results.

Glynn and Himsworth [41] describe a method for producing necrosis of the liver in rats by means of a protein-deficient diet. This necrosis has the clinical and pathologic features of massive acute necrosis of the liver.   It closely resembles acute yellow atrophy in human patients and progresses to a condition of scarring similar to that of nodular hyperplasia.   The onset of this acute necrosis is delayed thirty to one hundred days after institution of the experimental diet.   The necrotic process does not uniformly involve the liver; areas of total necrosis alternate with areas where the liver cells are apparently healthy.   The delay in onset and the haphazard distribution of lesions differentiate this nutritional necrosis of the liver from the immediate acute uniform zonal necrosis caused by many liver poisons (e. g., chloroform, carbon tetrachloride). This nutritional necrosis was found to be due to lack of casein in the diet, and the ·exhibition of methionine in a dose of 20 mg. per rat per day was completely protective.

Drill. and Loomis [42] report abnormal hepatic function in dogs as measured by excretion of sulfobromophthalein sodium after single injec-

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38. Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G.; Moore, J. E., and Sheehan, H. L.: Epidemiology of Infective Hepatitis, Lancet **2**:8 (July 1) 1944.

39. Peters, R. A.; Thompson, R. H. S.; King, A. J.: Williams, D. I., and Nicoli, C. S., with a statistical appendix by Greenwood, M., and Martin, W. J.: The Treatment of Post-Arsphenamine Jaundice with Sulphur-Containing Amino-Acids, Quart. J. Med. **14**:35 (Jan.) 1945.

40. Beattie, J., and Marshall, J.: Studies on Hepatic Dysfunction: II.   The Value of Sulphur-Containing Amino-Acids and Casein Digest in the Prevention of Post-Arsphenamine Jaundice, Brit. M. J. **2**:651 (Nov. 18) 1944.

41. Glynn, L. E., and Himsworth, H. P.: Massive Acute Necrosis of the Liver: Its Significance and Experimental Production, J. Path. & Bact. **56**:297 (July) 1944.

42. Drill, V. A., and Loomis, T. A.: Effect of Mapharsen on Bromsulphalein Retention in Normal Dogs, Proc. Soc. Exper. Biol. & Med. **58**:296 (April) 1945.

tions of oxophenarsine hydrochloride in large doses. Retention of sulfobromophthalein sodium was observed in 59 per cent of 17 normal dogs after a single injection of 60 mg. of this drug. Retention of dye occurred irrespective of dosage over a range of 2.7 to 9.1 mg. per kilogram. Animals showing retention of dye from the initial injection of oxophenarsine hydrochloride showed either less retention or a complete return to normal after subsequent injections. Dogs which initially showed a normal retention of dye also had normal retention following two subsequent injections.

In an attempt to determine whether the administration of bismuth interferes with recovery from hepatitis occurring during the course of arsenical therapy, Forbes [43] followed the hippuric acid excretion test on two groups of patients, one group receiving bismuth during the period of jaundice and the other receiving no form of antisyphilitic treatment. All patients had early syphilis and, except for the bismuth, received identical supportive treatment. In the 10 patients who received bismuth during the course of their illness, the recovery periods varied from 14 to 44 days (mean, 28.5 days). The recovery periods of 11 patients who received no bismuth varied from 19 to 48 days, with a mean of 34.4 days. Thus, in these small groups, the bismuth-treated patients recovered slightly more rapidly than those not receiving bismuth, but the difference is not considered to be statistically significant. Certainly the administration of bismuth did not retard recovery of hepatic function in these patients.

Nephrosis.—Heyman [44] says that the widespread use of bismuth in syphilotherapy and the paucity of reports of its toxic manifestations are evidence that bismuth therapy is relatively safe. It must not be assumed, however, that the use of bismuth is totally without danger, for there are recurring reports of deaths following its injection. Most of these fatalities are caused by the toxic effects of bismuth on the liver or kidney. Although such serious systemic reactions are uncommon, 4 patients with severe visceral manifestations of bismuth poisoning have been seen at Grady Hospital within the past few years. The most constant feature of their cases was the production of varying degrees of renal insufficiency following the administration of bismuth. This was manifested as anuria, azotemia, albuminuria and decreased excretion of phenol sulfonphthalein.

Although the nephrotoxic action of bismuth is known, its occurrence in some patients and not in others has not been fully explained. In

43. Forbes, J. R.: Bismuth Therapy in Jaundice During Antisyphilitic Treatment, Brit. M. J. **2**:852 (Dec. 30) 1944.

44. Heyman, A.: Systemic Manifestations of Bismuth Toxicity: Observations on Four Patients with Pre-Existent Kidney Disease, Am. J. Syph., Gonor. & Ven. Dis. **28**:721 (Nov.) 1944.

many cases renal complications occur in supposedly healthy adults after one or several injections of the drug. That preexistent renal damage may be a predisposing factor in bismuth poisoning has been repeatedly discussed in the literature. The prevalent impression among syphilologists is that with the usual doses employed the drug causes so few renal complications that it can be used for patients with previous renal disease. Although this may be generally true, there have been so many reports that such patients exhibit an intolerance to bismuth that further observation is warranted.

Treatment of Severe Arsenical Reactions.—To date, little has been published regarding the antiarsenical activity of BAL, a drug whose composition has not yet been made public, in the interests of national security. Certainly this drug holds promise in the treatment of the more serious arsenical reactions. The author of an article [45] in the *Bulletin of the United States Army Medical Department* says that BAL is a specific antidote for systemic arsenic poisoning. Once the diagnosis of arsenic poisoning has been made, BAL should be administered whether the poisoning is in an early or an advanced stage. An immediate intramuscular injection of 10 per cent BAL in oil should be given deep into the muscles of the buttocks. Dosage must be adjusted to body weight: 125 pounds (56.7 Kg.), 2.5 cc.; 150 pounds (68 Kg.), 3 cc.; 175 pounds (79.4 Kg.), 3.5 cc., and 200 pounds (90.7 Kg.), 4 cc. The injection should be repeated every four hours to a total of four doses. In cases of severe poisoning the interval between the first and second dose should be shortened to two hours and the course of therapy extended to include single daily half-doses for three or four days. BAL in oil causes certain reactions. These may include constriction in the throat, oppression in the chest, burning of the lips, reddening and lacrimation of the eyes, dryness of the mouth, nervousness and restlessness, nausea and vomiting and local tenderness. There may be a transient rise in blood pressure. These reactions do not as a rule contraindicate the continued administration of the full course of four injections of the drug.

Intensive Treatment of Early Syphilis.—In the course of a general review of chemotherapy Dale [46] remarks, in referring to the arsenical chemotherapy of syphilis:

And there comes thus to our notice another factor in an effective chemotherapeutic action, which has not always, I suspect, received sufficient attention—namely, the need for a sufficiently prolonged and continuous action. This need is almost implied in the conception of the process as essentially an arrest of the multiplication of the parasites rather than an immediately lethal action on them.

45. Acute Arsenic Poisoning, Bull. U. S. Army M. Dept., May 1945, no. 88, p. 13.
46. Dale, H.: A Prospect in Therapeutics, Brit. M. J. **2**:411 (Oct. 2) 1943.

What is required is not the sudden attainment of a concentration sufficient to kill most of the parasites, at the risk of a concomitant injury to the host's tissues, but the long-continued maintenance of a much lower and safer concentration, just sufficient to suppress the propagation of the parasites, without harming the cells of the host.

The importance of these sentences to investigators in the field of intensive arsenotherapy of syphilis and of penicillin treatment as well (to be discussed later) cannot be too strongly emphasized.

Neilson and his co-workers [47] treated 487 patients with early syphilis intensively for an average of five days, utilizing the continuous intravenous drip. Each patient received from 900 to 1,200 mg. of oxophenarsine hydrochloride. A second course was given to 15 patients. It was necessary to discontinue treatment in 23 patients because of severe toxic reactions. There were three separate treatment groups. The first received oxophenarsine hydrochloride alone; the second received, in addition, a single intramuscular injection of 5 cc. of 10 per cent bismuth subsalicylate in oil, and the third, six weekly injections of 150 mg. of bismuth in a follow-up clinic, in addition to the 5 cc. given in the hospital. There were 4 deaths from treatment among patients in whom intensive therapy was initiated, a fatality rate of 0.79 per cent. In 23 additional patients severe reactions were experienced that might have resulted in death if treatment had not been discontinued. Nonfatal reactions were frequent.

Results of treatment are reported for only 155 patients, since this was the total number followed for five months or longer. Of these, the reactions of 68.3 per cent had become seronegative; those of 10.3 per cent were almost seronegative; those of 3.2 per cent were still seropositive; 15 per cent had suffered serologic or mucocutaneous relapse, and 3.2 per cent had a presumed reinfection or superinfection.

Berry and Mitchell [48] report a follow-up study of the cases of 50 of 100 patients with early syphilis treated by the five day massive dose method. Twenty-three patients were followed for one to two years, 12 from two to three years, and 11 patients were followed over three years. The duration of follow-up of the remaining 4 patients is not stated. For only 4 is treatment classified as failure. Among the 100 patients treated there was 1 fatality due to hemorrhagic encephalitis. The only other serious complication was 1 case of toxic hepatitis and polyneuritis.

47. Neilson, A. W.; Blaney, L. F.; Stephens, L. J., and Maxwell, R. W.: Intensive Chemotherapy of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:553 (Sept.) 1944.

48. Berry, N. E., and Mitchell, L. I.: Four Years' Experience in Massive Dose Therapy of Early Syphilis, Canad. M. A. J. **51**:356 (Oct.) 1944.

Cannon and his co-workers[49] report the results of treating 332 patients with early syphilis with massive doses of arsphenamine by the syringe method. Treatment was carried out in the hospital over a period of five to six days. The drug was given in 2 per cent solution by the syringe method three or four times daily. The total dose ranged from 1.5 Gm. in the beginning of the experiment to a maximum of 4.4 Gm. Of the 332 patients treated, 178 have been followed from six months to three years. One hundred and eighteen patients (66 per cent) are clinically and serologically negative and have normal spinal fluids. Fifty-seven patients had an unsatisfactory outcome. Of these, 36 had cutaneous relapses. Of all the 178 patients only 27 failed to become serologically negative at some time during the period of observation. Of all the patients treated 12 had severe reactions. Two had encephalitis and recovered; 3 had hepatitis, and of these 1 died; 2 had exfoliative dermatitis: 3 had persistent neuritis, and 2 had blood dyscrasias. As a result of their experience, the authors conclude that the treatment of early syphilis with arsphenamine by the multiple syringe method over a period of five or six days is ineffective, dangerous, expensive and altogether impractical.

An account of the results of intensive arsenotherapy for early syphilis in the United States Army in the European Theater of Operations is presented by Pillsbury and his associates.[50] Intensive arsenotherapy was undertaken in April 1943 because of the difficulties of carrying out standard prolonged treatment for early syphilis under conditions of global warfare and because these difficulties caused serious interruptions in treatment which greatly reduced its effectiveness. The scheme of treatment consisted in the administration of a total of 20 mg. of oxophenarsine hydrochloride per kilogram of weight, given in twenty equal injections by the syringe technic over a twenty day period, plus eight injections of bismuth subsalicylate during the same time interval. In a series of 775 consecutive patients, treatment was completed for 96.3 per cent with no deaths. Data as to the result of treatment were incomplete, since only 435 patients had been followed for a minimum of four months. The authors have the impression, however, that the ultimate results will compare favorably with those obtained by prolonged methods of treatment.

Marin and Lambert[51] treated 62 patients with early syphilis by daily injections of 0.06 Gm. of oxophenarsine hydrochloride for thirty days.

49. Cannon, A. B.; Fisher, J. K.; Rodriguez, J. J.; Beattie, G. F., and Maechling, E.: Intensive Arsenotherapy, J. A. M. A. **126**:544 (Oct. 28) 1944.

50. Pillsbury, D. M.; Courville, C. J.; Crede, R. H.; Myers, J. E., and Wise, C. R.: The Intensive Therapy of Early Syphilis, Brit. J. Ven. Dis. **20**:154 (Dec.) 1944.

51. Marin, A., and Lambert, A.: A Thirty Days' Treatment of Early Syphilis (Preliminary Report), Canad. M. A. J. **51**:265 (Sept.) 1944.

Three months after cessation of treatment, 51 per cent were seronegative. Of 27 patients followed twenty to twenty-eight months only, 43 per cent were seronegative. Of 17 patients whose spinal fluids were examined, all were seronegative. Erythema of the ninth day was noted four times, icterus was noted once, and menace [sic] of malignant granulopenia was noted thirteen times.

Goldblatt [52] treated 104 men and 3 women with a total dose of 1,800 mg. of oxophenarsine hydrochloride. The drug was administered intravenously in daily doses of 60 mg. for thirty consecutive days. Of the entire group 27 had primary syphilis; 21, secondary syphilis; 17, late syphilis, and 7, congenital syphilis; in 35 the disease was latent. There were no fatalities, nor were any serious reactions encountered. Two patients had an erythema of the ninth day; neither was seriously ill. Twelve patients with primary syphilis were seronegative and remained so for the follow-up period. Eighty-one per cent of the group had positive serologic reactions for syphilis at the outset of treatment, and from three to six months after the termination of treatment 20 per cent of these remained seropositive and 8 per cent had doubtful reactions. Most patients were followed for six months, with but 1 exception, patients with infectious or latent syphilis who were followed had complete serologic reversal. There were three serologic relapses in the group.

As a result of extensive experimentation on animals and in an effort to treat early syphilis intensively yet safely, Eagle [53] enlisted the aid of a number of clinics to carry out treatment for a period of twelve weeks. Among other reasons, his paper is particularly valuable for the inclusion of a sound statistical method of approach, for which details are given. He summarizes the results of his study as follows:

1. A total of 4,823 patients, including 3,394 cases of primary and secondary, 1,190 of latent and 159 of recurrent or relapsing syphilis, have been treated and with triweekly injections of mapharsen at approximately 1 mg. per kilogram per injection, with a maximum of 80 mg. and a minimum of 40. Two thirds of the patients were given concomitant weekly injections of a bismuth compound, usually bismuth subsalicylate (0.2 Gm.).

2. Treatment had to be interrupted because of toxic reactions in a total of 106 patients. Thirty-nine of these were serious reactions, with jaundice the most common complication. Four patients died. It is believed that at least two of these deaths were preventable and the mortality of the triweekly schedule is on the order of 1:2,000. The incidence of toxic reactions was highest in young Negro women, and there were no deaths in the 2,583 men.

52. Goldblatt, S.: Intensive Ambulatory Therapy of Syphilis: Thirty Day Mapharsen Technic, Arch. Dermat. & Syph. **49**:403 (June) 1944.

53. Eagle, H.: The Treatment of Early and Latent Syphilis in Nine to Twelve Weeks with Triweekly Injections of Mapharsen: A Preliminary Analysis of the Results in the First 4,823 Cases, J. A. M. A. **126**:538 (Oct. 28) 1944.

3. Triweekly injections of mapharsen alone, without bismuth, gave uniformly poor therapeutic results, regardless of dosage.

4. Triweekly injections of mapharsen in conjunction with weekly injections of bismuth proved highly effective. In patients receiving an average total of 1,600 mg. (21 mg. per·kilogram or more) plus an average total of nine injections of bismuth, the cumulative percentage of treatment failure was 9.3 and the cumulative percentage of "cure" fifty to sixty weeks after the beginning of treatment was 82 per cent. A decrease in either mapharsen or bismuth to less than these amounts resulted in a higher proportion of treatment failure.

5. Although these results are tentative, based on the prolonged observation of as yet a small proportion of the total patients treated, it is believed that triweekly injections of mapharsen at approximately 1 mg. per kilogram, combined with weekly injections of 0.2 Gm. of bismuth subsalicylate and continued for nine to twelve weeks, will probably "cure" 85 to 90 per cent of cases of early syphilis.

6. (a) The initial reagin titer affected the rate at which seronegativity was obtained but did not affect the ultimate percentage "cured." (b) Within fairly wide limits (fifty-four to eighty-one days), the total duration of treatment also had no effect on the end results. Within that time period occasional lapses in treatment or smaller individual dosages could be ignored, provided the patient eventually received the scheduled total amount of drug. (c) With equal amounts of treatment, secondary syphilis gave significantly more treatment failures than did seropositive primary syphilis.

7. The efficacy of this schedule in the prevention of congenital syphilis, and its efficacy in latent syphilis, are under continued study.

The cooperating clinics of New York and the Midwest [54] have analyzed results for a group of 4,351 patients treated intensively for early syphilis. Only those patients were chosen whose infection was of less than four years' duration either with or without active manifestations of the disease. These patients were treated during the period from 1933 to 1943 inclusive. The analysis of results, however, deals only with primary or secondary syphilis. Six different methods of treatment are analyzed: namely, slow intravenous drip, neoarsphenamine; slow intravenous drip, oxophenarsine hydrochloride; rapid intravenous drip, oxophenarsine hydrochloride; multiple syringe injection, oxophenarsine hydrochloride; multiple syringe injection, oxophenarsine hydrochloride plus typhoid vaccine; multiple syringe injection, arsphenamine, and other miscellaneous methods (a very small group).

This work is well summarized by the anonymous authors as follows:

1. The therapeutic results in a group of 4,351 massive arsenical treatment for syphilis have been studied.

2. It was found that the best results (excluding the highly reactive slow intravenous drip administration of neoarsphenamine) followed the use of multiple syringe injection of mapharsen combined with typhoid vaccine.

54. Massive Arsenotherapy for Syphilis: United States Public Health Service Evaluation, Cooperating Clinics of New York and Midwestern Group, J. A. M. A. 126:554 (Oct. 28) 1944.

3. The most effective massive arsenotherapy yields 85 to 90 per cent of satisfactory results in primary syphilis. and 70 per cent in secondary syphilis.

4. About 5 to 6 per cent of the primary cases relapsed and 10 to 13 per cent of the secondary cases.

5. Patients treated when the titer of the Kahn quantitative test on the blood was 20 units or below experienced more frequent satisfactory results and fewer clinical relapses than did cases with a titer greater than 20 units.

6. Results were slightly better among patients receiving larger doses of arsenicals than among those receiving smaller doses.

The administration of bismuth during the period of treatment appeared to improve the results obtained.

8. The following differences in response to treatment were noted: Patients over 25 years of age responded better than those under 25; males responded better than females; whites responded better than nonwhites.

9. Least satisfactory results to treatment were obained among young nonwhite females.

10. Acute encephalopathy was observed in 7.1 per thousand treatments. Of these 3.2 per thousand were fatal and 3.9 per thousand were followed by recovery. No difference could be demonstrated between treatments with regard to the frequency of this type of reaction.

Alexander and Schoch,[55] who have had much personal experience in the intensive treatment of early syphilis, review some of the more important contributions to this subject and conclude that longer term methods of intensive arsenotherapy of early syphilis, which do not require hospitalization of patients, should be used in preference to the hazardous and highly technical short term methods. Results of treatment are satisfactory with all methods. The twenty-six week method used by the Army of the United States, the triweekly twelve week schedule suggested by Eagle[53] and perhaps the twenty to thirty day syringe method can be advocated for general use on ambulatory patients.

Thomas and Wexler[56] review the results of 2,144 courses of rapid treatment for early syphilis, utilizing oxophenarsine hydrochloride administered by the multiple syringe technic, with or without the addition of fever therapy induced by typhoid vaccine. The injection of more than 1 Gm. of oxophenarsine hydrochloride in a period of six to ten days was associated with toxic encephalopathy in over 1 per cent of the patients treated. There were 3 deaths in 909 courses of treatment. The maximum daily dose of oxophenarsine hydrochloride was, therefore, subsequently fixed at 1 mg. per kilogram of weight, and the period of treatment was extended to at least ten days.

55. Alexander, L. J., and Schoch, A. G.: Intensive Arsenotherapy of Early Syphilis: Experience with over 1,300 Treated Patients, and a Review of the Literature, Clinics **3**:960 (Dec.) 1944; Newer Developments in Syphilis Therapy, South. M. J. **37**:705 (Dec.) 1944.

56. Thomas, E. W., and Wexler, G.: Review of 2,144 Courses of Rapid Treatment for Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:529 (Sept.) 1944.

Combined Fever and Arsenotherapy.—In formulating their schedules of therapy in a later paper, Thomas and Wexler [57] consider not only the total amount of oxophenarsine hydrochloride which can safely be given in five to ten days but also the maximum single dose which can prudently be given at daily intervals. It was found that the maximum single dose of oxophenarsine hydrochloride per day was practically 1 mg. per kilogram of weight and the minimum period of treatment ten days. With such a schedule, the average patient received ten daily injections of about 60 mg. of oxophenarsine hydrochloride. To reenforce treatment with this low dosage, four fever treatments were given on the second, fourth, sixth and eighth days, produced by the intravenous injection of typhoid-paratyphoid combined vaccine. The first fever was induced with an injection of 0.1 cc. of vaccine, the second with 0.2 cc., the third with 0.4 cc. and the last with 0.6 cc. From one and one-half to two hours after each of these injections a booster dose was administered, usually of an equal amount. Although the fever response to this amount of vaccine varied, it generally caused a temperature of 104 F. for about four hours. Later bismuth was added to the scheme of treatment, and 0.1 Gm. of bismuth subsalicylate in oil was administered on the first, third, seventh and tenth days of therapy.

By May 1, 1944, 1,163 courses of treatment had been given according to this plan, without a single fatality. There were only 3 cases of mild encephalopathy and 1 case of granulocytopenia, from which the patient completely recovered. However, by the time 1,181 courses of treatment were completed there was 1 fatality, from hemorrhagic encephalitis. Therefore, in 1,181 treatments there were 4 cases of encephalopathy (0.34 per cent) and 1 death (0.08 per cent).

There were 772 patients with early syphilis treated. However, only 435 (56.3 per cent) had been followed from six to thirty-eight months. The results for 351 (80.7 per cent) were probably favorable.

Jones and his co-workers [58] report further observations on the one day treatment of early syphilis (combined fever and chemotherapy). Three methods have been given clinical trial. Schedule A consisted of 1 mg. of oxophenarsine hydrochloride per kilogram of weight, administered during the induction period of the fever. With schedule B, 1 mg. of oxophenarsine hydrochloride per kilogram of weight was injected in the evening prior to fever therapy, and a second injection, this time in the amount of 1.5 mg. per kilogram of weight, administered at the termination of fever. In schedule C, 2 mg. of oxophenarsine hydrochloride per kilo-

57. Thomas, E. W., and Wexler, G.: Combined Fever and Arsenotherapy in the Intensive Treatment of Early Syphilis, J. A. M. A. **126**:550 (Oct. 28) 1944.

58. Jones, N.; Hundley, J. L., and Walker, A. E.: Further Observations on One Day Treatment of Syphilis with Fever and Mapharsen, New York State J. Med. **45**:277 (Feb. 1) 1945.

gram of weight was administered at the termination of fever. With all three schedules, fever therapy consisted of five hours at a body temperature of 41.1 C. (106 F.).

The results of these three methods of therapy were as follows: Seventy-eight patients were treated according to schedule A and followed for twenty-two to thirty months; of these, 15 (19 per cent) had a clinical relapse and 1 a serologic relapse; 6 additional patients were thought to have been reinfected. Of 137 patients treated with schedule B and followed for twelve to twenty-two months, 13 (10 per cent) had a clinical relapse and 3 (2 per cent) showed serologic relapse; 2 patients were considered probably to have been reinfected. Two hundred and six patients were treated according to schedule C and observed for three to nine months; 16 (8 per cent) of these have shown clinical relapse during this short period of follow-up, and 5, serologic relapse. Only half the patients in this group, however, had symptomatic early syphilis, the others having early latent syphilis. The percentage of seroresistant patients is not indicated, nor does the report indicate the percentage of patients lost from observation.

During the period from 1932 to 1940 Kendell and his co-workers [59] treated 77 patients with primary or secondary syphilis with combined artificial fever and chemotherapy. During the first six years the course consisted of approximately fifty hours of fever maintained at an average temperature of 105.8 F. (rectal), usually given in ten weekly sessions of five hours each. From 1937 to 1940 the course comprised an average of twelve shorter sessions (three hours), usually at more frequent intervals, for an average total of thirty-six hours of fever maintained at the same average temperature. The two groups responded similarly. The authors do not provide details as to the chemotherapy used for these patients.

Of the 77 patients 17 were lost from observation. The remaining 60 patients were followed for two to ten years. Eight patients with seronegative primary syphilis remained clinically and serologically negative. Of the 24 patients with seropositive primary syphilis, 22 exhibited a rapid and progressive decline to negativity, both clinically and serologically. Of the 20 patients with early secondary syphilis all but 2 achieved clinical and serologic negativity after treatment. In the group of 8 patients with secondary manifestations occurring during the first or the second year of the disease, 5 responded both clinically and serologically.

In 1940 the authors began an investigation to determine whether it might be possible to cure syphilis in one day. Thirty-seven patients with unequivocal early syphilis, positive on dark field examination,

59. Kendell, H. W.; Rose, D. L.; Miller, E., and Simpson, W. M.: Artificial Fever and Chemotherapy in Early Syphilis, Arch. Phys. Med. 26:76 (Feb.) 1945.

were included in this study. Six had secondary syphilis, and the remaining 31 had primary syphilis. The following treatment was instituted:

Just before the fever treatment was begun, 0.256 Gm. of bismuth subsalicylate was administered. The patient was then placed in the hypertherm and given one ten hour session of fever at 106 F. (rectal). Seven patients received 240 mg. of oxophenarsine hydrochloride by intravenous drip during the fever session. This procedure was later changed in favor of ·administration of the drug by syringe in doses of 40 or 60 mg. to a total of 120 mg. to 160 mg. No other treatment was administered subsequently. Six patients were followed for four to six months; 29 were followed for six months to two and one-half years; 1 patient was lost to follow-up, and 1 died as a result of treatment. All of the 35 patients who were followed are now clinically and serologically negative.

The authors say that intensification of the fever-chemotherapy method as described increases complications, and they do not recommend this method as routine for the treatment of early syphilis.

Schwemlein, Kendell and Craig [60] present the methods of charting used during the past twenty-three months at the Chicago Intensive Treatment Center in the artificial fever-chemotherapy of 1,667 patients with early syphilis. The actual chart utilized, with explanatory comments, presented in the original article, does not lend itself to reproduction. The value of this system is that it presents a quick summary of the patient's condition under treatment every fifteen minutes. As the readings are chronologic, valuable information is afforded for the investigation and control of the patient's water and electrolyte balance.

The results of treatment of early syphilis with bismuth alone are reported by Sharp, Dickerson, Sevier and Branch.[61] The drug, bismuth ethylcamphorate, was injected intramuscularly twice weekly in 2 cc. doses (80 mg. of metallic bismuth). One group consisting of 41 patients with untreated early syphilis were treated in this manner for eight weeks. A second, of 30 patients with infectious (9 patients) or serologic (21 patients) relapse following intensive arsenotherapy, were so treated for thirteen to sixteen weeks. At the time of this report all patients had been followed a minimum of eight months. Of the first group, all 41 patients were considered to have attained clinical and serologic "cure." Of the second group (30), all had remained clinically well, and all but 5 had become seronegative. No toxic reactions were observed.

(To Be Concluded)

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60. Schwemlein, G. X.; Kendell, H. W., and Craig, R. M.: Artificial Fever-Chemotherapy: III. Charting Procedures, Arch. Phys. Med. **26**:8 (Jan.) 1945.

61. Sharp, J. W.; Dickerson, M. S.; Sevier, M., and Branch, W.: Intensive Bismuth Ethylcamphorate Treatment of Early Syphilis and Its Use in Relapse Cases, Urol. & Cutan. Rev. **48**:613 (Dec.) 1944.

Book Reviews

The Avitaminoses: The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By Walter H. Eddy, Ph.D., and Gilbert Dalldorf, M.D. Price, $4.50. Pp. 438, with 40 tables and 46 figures. Baltimore: The Williams & Wilkins Company, 1944.

Fifteen years ago Dr. Eddy wrote a book entitled "The Vitamine Manual." A comparison of that book with the present, or third, edition, under a new title, will indicate that this new edition is larger and much more complete than the first, chiefly because of the addition of most important pathologic and somewhat less important clinical discussions of vitamin deficiency diseases. Secondly, the third edition indicates the tremendous amount of work, both clinical and in the laboratory, which has been done by investigators throughout the world in the study of vitamins and the avitaminoses.

This edition is divided into three parts, the first dealing with the various vitamins known to the clinician by letters and including a chapter on the nature and function of vitamin E and one on vitamin K, as well as a similar chapter on "bios nutralites." Vitamin B as such is not included among the vitamins, but chapters are devoted to thiamine, riboflavin, niacin and pyridoxine.

Part two is devoted to the avitaminoses and describes the clearcut syndromes which arise as a result of an insufficient amount of this or that vitamin in the dietary intake, such as pellagra, scurvy, rickets or other vitamin deficiency disorders. It seems rather a pity that the author has not included a section on multiple deficiencies, which do not present a clearcut syndrome of any one vitamin deficiency but which in the aggregate, because of the inadequate intake of numerous vitamins and other necessary nutritional elements, present a bizarre picture of disease or of functional disorder.

The third portion of the book has to do with technical methods of vitamin assay; then there follows a bibliography of some 32 pages and an appendix indicating the vitamin content of various foods and a second table which lists the known facts concerning the as yet incompletely assayed members of the B complex, those other than thiamine, riboflavin and niacin (nicotinic acid).

One cannot do otherwise than speak well of this book. The clinician can use it, and the man in the laboratory can obtain much information from it. Its success seems assured.

Bronquiectasias. By Dr. Mariano R. Castex, Professor of Clinical Medicine, Faculty of Medicine of Buenos Aires, and Dr. Egidio S. Mazzei, Assistant Professor of Clinical Medicine of La Plata. Paper. Price not given. Pp. 77, with 19 illustrations. Barcelona-Buenos Aires: Salvat Editores, S. A.

This monograph, one of the *Manuales de Medicina Practica,* gives a vivid description of the clinical types of bronchiectasis seen in Argentina, including roentgenographic observations and discussions of the physiopathology of the disease, certain pathologic features and therapeutic methods. The structure of the bronchi was studied by bronchography with opaque oil, by tomography and by a special photographic technic called "broncorrelievografía," by which means minute details of the bronchi filled with opaque oil were sharply demonstrated. The morphologic types of bronchiectasis are classified as (1) cylindric, (2) ampullaceous, (3) saccular and (4) maniliform. The authors found that the acquired form occurred more frequently than did the congenital, and they postulate that chronic infections are the most important causes of the acquired forms. No favorite methods of

therapy are especially advocated. Bronchoscopic examinations or treatments were apparently not often utilized. No enthusiasm is expressed for lobectomy.

An extensive bibliography is appended. An unusually large proportion of the references are to the French literature.

It is pleasant to receive such well prepared material from our southern neighbors, and it is hoped that similar articles in the future will contain statistical information as regards incidence, attack rate, percentage of patients treated by various methods and results obtained, mortality and so forth, so that one may compare similar problems in the various countries.

A Synopsis of Medicine. By Sir Henry Letheby Tidy, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.). Eighth edition. Price, $7.50. Pp. 1,215. Baltimore: The Williams & Wilkins Company; Bristol: John Wright & Sons, Ltd., 1945.

It is rather interesting to note that in the preface to the first edition of this book, which appeared in 1920, the author stated that there was a long interruption due to the war, the book appearing several years after the original date of its intended publication. In the eigthth, and present, edition it is noted that the revision of this edition has been accomplished with difficulty; ". . . the premises of the publisher have been twice damaged severely by enemy action, on one occasion unfortunately with serious loss of life. Several thousands of copies of a reprint were destroyed by enemy action." It seems remarkable that this book of Tidy's has successfully survived two world wars, both of which interfered materially with its publication.

This is a standard synopsis which has been used for many years by practitioners and students of medicine. The reviewer has little quarrel with the author concerning the material contained between the two covers of this book. One definite criticism would be that the space assigned to the various diseases is by no means proportional to their importance. This is a real criticism, as the book is certainly too large in its present form and is difficult to handle. In support of the statement of the disproportionate amount of space given to certain diseases, it might be noted that of the first 50 pages (chapter 1), 34 are devoted to typhoid and 14 to diphtheria, while erysipelas has one page and septicemia, pyemia and toxemia taken as a whole have a little over a page devoted to them. Lobar pneumonia occupies 17 pages, whereas a page only is given to primary atypical pneumonia, which, in the United States at least, has been seen much more frequently of late than has the classic pneumococcic pneumonia.

There are a few statements which are incorrect and undoubtedly will be revised in the next edition. As an example, Streptococcus scarlatinae is given as the cause of scarlet fever, whereas it is only one of a number of hemolytic streptococci which may produce the symptoms of this disease.

The book purely as a synopsis is highly recommended to persons who wish to make use of this type of publication. Certainly it will prove a timesaver to the general practitioner, as the author indicates in his preface. Whether or not the immense amount of material contained in the book, for the most part presented in telegraphic style, could be assimilated and remembered in a short time by the "worried student whose final examinations are within sight" is a question.

Hayfever Plants. By Roger P. Wodehouse. Price, $4.75. Pp. 245. Waltham, Mass.: The Chronica Botanica Co.; New York: G. E. Stechert and Company, 1945.

This thorough compendium deals in a systematic way with the botany and geography of the various plants concerned with hay fever. Supplemented by regional surveys which make up the latter part of the book, it is an invaluable encyclopedia for the physician who deals with allergic disease. There are numerous illustrations, a bibliography and an index.

RESULTS IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

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AND

NED McKRILL, M.D.[†]

NEW ORLEANS

R ESULTS in the treatment of subacute bacterial endocarditis with a wide variety of therapeutics measures were uniformly unsuccessful prior to the advent of the newer chemotherapeutic drugs. Methods of therapy in recent years have included the use of arsenicals as employed by Osgood,[1] heparin alone,[2] sulfonamide compounds in usual[3] and massive dosages,[4] sulfonamide drugs and heparin,[5] sulfonamide drugs and artificial fever induced by typhoid vaccines[6] or by physical measures, and penicillin alone and in combination with heparin. Lichtman,[7] in reviewing 704 cases (fig. 1), found 1 per cent of spontaneous cures. Of 489 patients treated by sulfonamide chemotherapy, 21 recovered, an incidence of 4 per cent; of 109 heparinized, 7 (6.5 per cent) recovered; of 61 patients given artificial fever therapy, 4 (6.5 per cent) recovered; of 45 patients treated with chemotherapy and intravenously injected typhoid vaccine, 7 (15.5 per cent) recovered.

1. Osgood, E. E.: Neoarsphenamine Therapy of Bacterial Infections, Arch. Int. Med. **69**:746 (May) 1942.

2. Friedman, M.; Hamburger, W. W., and Katz, L. N.: The Use of Heparin in the Therapy of Subacute Bacterial Endocarditis, J. A. M. A. **113**:702 (Nov. 4) 1939.

3. Field, H.; Hoobler, S. W., and Avery, N. C.: Results of Chemotherapy in Subacute Bacterial Endocarditis, Am. J. M. Sc. **202**:798, 1941.

4. Dick, G. F.: Subacute Bacterial Endocarditis: Recovery Following Intravenous Sodium Sulfadiazine, J. A. M. A. **120**:24 (Sept. 5) 1942.

5. Kelson, S. R.: New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination: Preliminary Report, J. A. M. A. **113**:1700 (Nov. 4) 1939.

6. Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment With Sulfapyridine and Intravenous Injections of Typhoparatyphoid Vaccines, New York State J. Med. **41**:45, 1941.

7. Lichtman, S. S.: Treatment of Subacute Bacterial Endocarditis: Current Results, Ann. Int. Med. **19**:787, 1943.

Heparin was first employed in the treatment of endocarditis by Friedman, Hamburger and Katz,[2] and Kelson and White.[8] Katz and Elek[9] concluded from their series treated with heparin and chemotherapy that the use of heparin should be abandoned. They administered heparin to a patient for six weeks without ill effects. Friedman,[10] Blumer,[11] and Smith, Sauls and Stone[12] have also expressed their

% RECOVERIES

CHEMOTHERAPY AND INTRAVENOUS TYPHOID	15.5
CHEMOTHERAPY AND ARTIFICIAL FEVER	6.5
CHEMOTHERAPY AND HEPARIN	6.5
SULFONAMIDE	4.0
(SPONTANEOUS REMISSION)	1.0

% 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
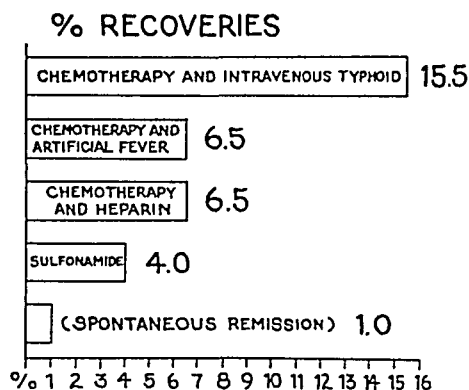
Fig. 1.—Results in the treatment of subacute bacterial endocarditis reported by Lichtman.

TABLE 1.—*Results of Treatment of Subacute Bacterial Endocarditis with Penicillin Reported by Other Authors*

Author	Number of Cases	Number of Probable Cures
Florey and others [17]	1	1
Keefer, C. S.[16]	55	3
Herrell and others [18]	4	0
Roy, B. B.[19]	17	3
Collins, B. O.[20]	1	1
Bloomfield and others [21]	10	8
Pizzi and associate [22]	1	1
Dawson and associate [14]	27	21
White and others [23]	9	6
Loewe [24]	54	40
Kelson [25]	1	1
Harford and others [26]	3	2
Paullin and associate [27]	6	3
Meads and others [15]	9	7
Evans [27]	4	1
Russek and others [28]	2	2
Seabury [29]	12	8
Traut, E. F.[30]	1	1
Goerner [32]	16	11
Bloomfield and others [33]	11	10
Hines and associate [34]	2	0
Flippin and others [31]	20	16
Levy and associate	11	8
Total	277	154 (55.6%)

8. Kelson, S. R., and White, P. D.: Notes on 250 Cases of Subacute Bacterial (Streptococcal) Endocarditis Studied and Treated Between 1927 and 1939, Ann. Int. Med. **22**:40, 1945.

9. Katz, L. N., and Elek, S. R.: Combined Heparin and Chemotherapy in Subacute Bacterial Endocarditis, J. A. M. A. **124**:149, (Jan. 15) 1944.

10. Friedman, M.: The Use of Sulfanilamide and Sulfapyridine in the Therapy of Subacute Bacterial Endocarditis, Arch. Int. Med. **67**:921 (May) 1941.

opinion that the proved dangers of heparin therapy outweigh its unproved advantages. Lichtman in his review found a 6.5 per cent recovery rate with chemotherapy and heparin, a 2.5 per cent increase as compared to those cases in which chemotherapy alone was used.

Successful penicillin therapy in a series of cases of subacute bacterial endocarditis was first reported by Loewe and others [13] in January 1944. Dawson and Hunter [14] employed combined penicillin and heparin therapy in the majority of their 20 cases. Hemorrhagic complications resulting from heparinization were definitely observed in only 1 instance. Penicillin and heparin were employed in 5 of the 16 cases reported by Meads and his associates.[15] They concluded that no additional benefit was derived from its use. Hemorrhagic manifestations, noted by Meads during the administration of penicillin and heparin, occurred in 4 patients during treatment with penicillin alone. If we combine the cases reported by Keefer,[16] Florey,[17] Herrell,[18] Roy,[19] Collins,[20] Bloomfield,[21] Pizzi,[22] Dawson,[14] White,[23] Loewe,[24] Kelson,[25] Harford,[26]

11. Blumer, G.: Subacute Bacterial Endocarditis, Medicine 2:105, 1923.

12. Smith, C.; Sauls, H. C., and Stone, C. F.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans, J. A. M. A. 119:478 (June 6) 1942.

13. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis: Report of Seven Consecutive Successfully Treated Patients, J. A. M. A. 124:144 (Jan. 15) 1944.

14. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. A. M. A. 127:129 (Jan. 20) 1945.

15. Meads, M.; Harris, H. W., and Finland, M.: The Treatment of Bacterial Endocarditis with Penicillin, New England J. Med. 232:463, 1945.

16. Keefer, C. S., in discussion on papers of Dawson and Hobby, Herrell, Bloomfield, Rantz and Kirby and Dubos, J. A. M. A. 124:636 (March 4) 1944.

17. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet 1:387, 1943.

18. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of 150 Cases in Which It Was Employed, J. A. M. A. 125:1202 (Aug. 26) 1944.

19. Roy, B. B.: Chemotherapy of Bacterial Invasion by Antibacterial Substances of Bacteria and Moulds with Special Reference to Penicillin, J. Indian M. A. 13:309, 1944.

20. Collins, B. C.: Subacute Bacterial Endocarditis Treated with Penicillin, J. A. M. A. 126:233 (Sept. 23) 1944.

21. Bloomfield, A. L.; Kirby, W. M. M., and Armstrong, C. D.: A Study of "Penicillin Failures," J. A. M. A. 126:685 (Nov. 11) 1944.

22. Pizzi, F. W., and McCarthy, F. W.: Subacute Bacterial Endocarditis Sucessfully Treated with Penicillin, U. S. Nav. M. Bull. 43:1010, 1944.

23. White, P. D.; Mathews, M. W., and Evans, E.: Notes on the Treatment of Subacute Bacterial Endocarditis Encountered in 88 Cases at the Massachusetts General Hospital During the Six Year Period 1939 to 1944 (Inclusive), Ann. Int. Med. 22:61, 1945.

Paullin,[27] Meads,[15] Evans,[27] Russek,[28] Seabury,[29] Traut,[30] Flippin,[31] Goerner,[32] Bloomfield,[33] Hines,[34] and Levy (table 1), there is a total of 154 (55.6 per cent) possible cures in 277 of the cases of subacute bacterial endocarditis treated with penicillin.

METHODS OF TREATMENT AND RESULTS IN THE CHARITY HOSPITAL

Table 2 shows the results that we secured at the Charity Hospital in the treatment of subacute bacterial endocarditis prior to the use of penicillin and heparin. Endocarditis was the cause of death in 0.6

TABLE 2.—*Results of Treatment in the Charity Hospital Prior to Penicillin Therapy*

	Cases	Successes	Failures
Supportive care alone	35	0	35
Sulfanilamide	20	0	20
Sulfadiazine	40	0	40
Other sulfonamide drugs	15	0	15
Sulfadiazine and fever	7	0	7
Sulfadiazine, massive dosage	4	0	4
Massive arsenotherapy	3	0	3

24. Loewe, L.: The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis, Canad. M. A. J. **52**:1, 1945; The Combined Use of Anti-Infectives and Anticoagulants in the Treatment of Subacute Bacterial Endocarditis, Bull. New York Acad. Med. **21**:59, 1945.

25. Kelson, S. R.: Observations on the Treatment of Subacute Bacterial (Streptococcal) Endocarditis Since 1939, Ann. Int. Med. **22**:75, 1945.

26. Harford, C. G.; Martin, S. P.; Hageman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococci, Pneumococci, Gonococci and Other Infections With Penicillin, J. A. M. A. **127**:325, (Feb. 10) 1945.

27. Evans, quoted by Paullin, J. E., and McLoughlin, C. J.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, Ann. Int. Med. **22**:475, 1945.

28. Russek, H. I.; Smith, R. H., and Derman, H.: Penicillin in the Treatment of Subacute Bacterial Endocarditis, Ann. Int. Med. **22**:863, 1945. Russek, H. I.; Smith, R. H., and Zohman, B. L.: Subacute Bacterial Endocarditis Complicated by Agranulocytosis: Report of Case with Recovery, ibid. **22**:867, 1945.

29. Seabury, J. H.: Personal communication to the authors.

30. Traut, E. F.: Treatment of Subacute Bacterial Endocarditis: Recovery with Penicillin, Illinois M. J. **88**:24, 1945.

31. Flippin, H. F.; Mayock, R. L.; Murphy, F. D., and Wolferth, C. C.: Penicillin in the Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **129**:841 (Nov. 24) 1945.

32. Goerner, J. R.; Geiger, A. J., and Blake, F. G.: Treatment of Subacute Bacterial Endocarditis with Penicillin: Report of Cases Treated Without Anticoagulant Agents, Ann. Int. Med. **23**:491, 1945.

33. Bloomfield, A. L.; Armstrong, C. D., and Kirby, W. M.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. Clin. Investigation **24**:251, 1945.

34. Hines, L. E., and Kessler, D. L.: The Effect of Penicillin on Heparin Tolerance, J. A. M. A. **128**:794 (July 14) 1945.

per cent of 8,313 cases in which autopsies were performed from 1935 to 1940 inclusive and in 5 per cent of the deaths due to heart disease. During the six and a half year period beginning in 1938, there were 112 clinical cases, or an approximate incidence of 1 in every 3,500 hospital admissions. Prior to the institution of penicillin and heparin therapy, there were no recoveries with supportive therapy, sulfonamide compounds in massive doses or arsenotherapy. Various other methods were used in a few cases not recorded.

Our original plan of treatment of subacute bacterial endocarditis consisted of the simultaneous administration of penicillin, heparin and sulfadiazine. Nine of our 11 patients received heparin dissolved in 1,000 cc. of a 5 per cent solution of dextrose in distilled water as a continuous intravenous drip along with penicillin intramuscularly for the initial two weeks of treatment. The amount of heparin given intravenously required to maintain a clotting time between thirty to sixty minutes for twenty-four hours has varied from 90 to 300 mg. (9 to 30 cc.). It has been our custom to dissolve one half of the estimated amount of heparin in a liter of a 5 per cent solution of dextrose in distilled water and start this as an intravenous drip. Regulation of the clotting time is then carried out by speeding or slowing the infusion, adding heparin to the infusion if the clotting time is low or connecting the solution of 5 per cent dextrose in distilled water without heparin to the infusion set if the clotting time is too high. In this manner the patient receives 2,000 cc. of fluid intravenously daily. We attempt to limit oral fluids during heparinization. The employment of penicillin and heparin in our infusions has not prevented the occasional occurrence of thrombophlebitis and the frequent occurrence of phlebothrombosis.

We have experienced frequent reactions during heparinization, occurring daily in some patients. These reactions are characterized by fever, sometimes with a temperature up to 108 F., chills, mild excitement and some disorientation. In an attempt to evaluate the etiologic agents responsible for these reactions, we have alternated the following procedures when patients experienced reactions: We have continued the infusion, utilizing the same tubing but employing a fresh bottle of heparin with a 5 per cent solution of dextrose in distilled water. We continued to utilize the same bottle of heparin with the dextrose in distilled water and changed the tubing, changed the site of the infusion, utilizing the same tubing with the 5 per cent solution of dextrose in distilled water without heparin, stopped the infusion and used various other modifications. All of these procedures were evaluated on each patient when he had a reaction, if the reaction was not too severe. If a severe reaction occurred the infusion was discontinued until the patient completely recovered, at which time it was again begun. These reactions did not necessitate permanent discontinuance of heparin in any

case, although it made clotting times irregular in some. From these studies it was concluded that varying factors come into play in causing these reactions. Some are pyrogenic reactions due to the release of protein from the decomposition of bacteria or to other foreign protein matter present in the infusion apparatus or infusion fluids. Some are due to heparin sensitivity, some are due to embolic phenomena, and some are not explainable. Undoubtedly the continuous flow of heparin and fluid over a piece of tubing for four days will tend to dislodge every minute particle of foreign matter from the tubing. Probably during the ordinary course of four hours with the same infusion set a reaction would not occur. It is difficult to determine the exact cause of the reaction in many cases, and if the reaction becomes too severe the infusion is temporarily discontinued. We have had only 1 case in our series in which deleterious effects may have been due to heparin.

Many of the unfortunate reactions occurring during heparinization are due to inadequate supervision of its administration. Determination of clotting time by the Lee and White method [35] should be made three times daily during the period of heparinization. The clotting time in 1 patient was eight minutes by other methods and sixty minutes by this method. We endeavor to maintain a clotting time between thirty and sixty minutes for a period of two weeks. The danger from overheparinization is greater from the tenth to the fourteenth day, that is, in the latter part of the treatment, than it is during the earlier part of the heparinization. If the clotting time rises to two hours during the first few days of treatment no serious consequences are likely to occur. However, later in the treatment elevated clotting times above sixty minutes are to be avoided. During the last few days of heparinization we try to keep the clotting time at the lower level of the margin of safety, that is, around thirty minutes. We have had no experience with heparin modified in various mediums, such as Pitkin menstruum, for subcutaneous implanation as utilized by Loewe and others.[36]

We have employed penicillin in varying dosages. At first we had to use smaller doses due to our limited supply. We realized the need for larger dosages than we were employing; however, an adequate supply of penicillin was not available to us for the treatment of subacute bacterial endocarditis when the initial portion of this work was started. Earlier we utilized the intravenous route of administration of penicillin, using heparin and penicillin in the same infusion. Because of the reactions to heparin, we frequently had to discard a bottle containing penicillin and heparin. Separate infusions of penicillin and of

35. Gradwohl, R. B. H.: Clinical Laboratory Methods, ed. 3, St. Louis, C. V. Mosby Company, 1943, p. 514.

36. Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin: Preliminary Report, Am. J. M. Sc. **208**:54, 1944.

heparin would render the treatment too undesirable both for the patient and for the physician. The incidence of thrombosis is increased when penicillin is used intravenously. As shown by Cowan,[37] some samples of rubber tubing inactivate some of the penicillin in the solution, especially when the penicillin is kept in contact with the rubber tubing for several hours. These reasons led us to the discontinuation of the intravenous route and the utilization of the intramuscular route, which rendered the treatment relatively simple except for the initial two weeks of heparinization. Penicillin was given in divided doses every two hours intramuscularly, in amounts varying from a total of 100,000 to 200,000 units daily. Two hour administration maintains a satisfactory constant level of penicillin.[38] We occasionally noted local reactions at the site of injection; these have become rare with the newer supply of penicillin. Penicillin levels in the blood were not determined. We did not perform penicillin sensitivity tests on the organisms isolated from our patients.

Sulfadiazine in a dosage of 1 Gm. every four hours day and night was employed along with penicillin and heparin. This was used because of the potentiation in the effect of penicillin noted by Rammelkamp,[38] Ungar,[39] and others [40] when its use was combined with the simultaneous administration of sulfadiazine. Daily urinalyses and triweekly complete blood counts were made, and the patients were watched closely for any signs of reaction to the sulfonamide drugs. The only reaction noted was a mild leukopenia in 1 case, which cleared rapidly on the discontinuation of the sulfonamide drug. Occasionally we kept our patients on a small maintenance dosage of sulfadiazine (1 Gm.) for a period of months following completion of treatment.

Figure 2 demonstrates our earlier plan when a limited amount of penicillin was available. Treatment was given for only fourteen days, 200,000 units of penicillin being given every twenty-four hours by continuous intravenous drip. During the first ten days, heparinization by continuous intravenous drip of 100 to 200 mg. of heparin for twenty-four hours was given in order to maintain the clotting time above thirty minutes.

37. Cowan, S. T.: Effect of Rubber Tubing on Solutions of Penicillin, Lancet **1**:178, 1945.

38. Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus, J. Clin. Investigation **22**:649, 1943.

39. Ungar, J.: Synergistic Effect of Para-Aminobenzoic Acid and Sulfapyridine on Penicillin, Nature, London **152**:245, 1943.

40. Bigger, J. W.: Synergic Action of Penicillin and Sulphonamides, Lancet **2**:142, 1944.

Figure 3 demonstrates the method employed in our later cases. Twelve thousand units of penicillin was administered day and night every two hours by intramuscular injections and was continued for twenty-eight days. Over this same period 1 Gm. of sulfadiazine was given every four hours day and night. Heparinization was accomplished during the first fourteen days by the same technic used in our previous cases. At present we are employing the method depicted in figure 3 with one modification: The dosage of penicillin has been increased to

PENICILLIN 200,000 UNITS EVERY 24 HR.
CONTINUOUS I.V. DRIP

HEPARIN 100 – 200 MGM. EVERY 24 HR.
CONTINUOUS I.V. DRIP (C.T. ↑ 30 MIN.)

DAYS–1 2 3 4 5 6 7 8 9 10 11 12 13 14
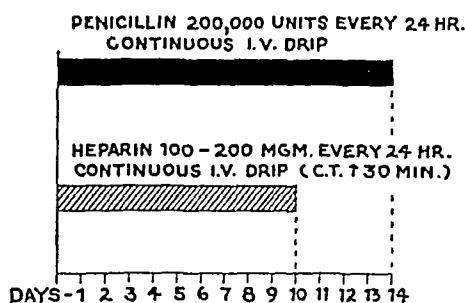
Fig. 2.—First method of penicillin therapy employed.

approximately 200,000 units daily. We are now using 17,000 units intramuscularly every two hours day and night. These patients received transfusions whenever their hemoglobin levels indicated the need for blood.

PENICILLIN 144,000 UNITS EVERY 24 HR.
I.M. 12,000 UNITS EVERY 2 HR.

SULFADIAZINE 1 GM. EVERY 4 HR.
D. AND N. ORALLY

HEPARIN 100–200 MGM. EVERY 24 HR.
CONTINUOUS I.V. DRIP (C.T. ↑ 30 MIN.)

DAYS – 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
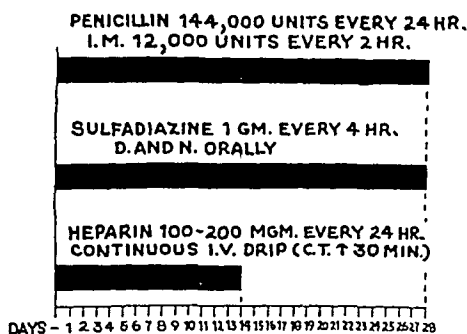
Fig. 3.—Second method of penicillin therapy employed.

Figure 4 shows an example of the record made for each patient. The amount and the time of administration of penicillin and heparin were recorded. Lee and White clotting times were determined at 8 a. m., 3 p. m. and 10 p. m. every day. Daily urinalysis and blood cultures were made, along with complete blood counts, three times a week. Accurate measurements of the patient's urinary intake and output were made daily. Any reactions which occurred were fully described on these charts.

All of our patients with endocarditis presented a history and had physical findings on auscultation of the heart compatible with either rheumatic or congenital heart disease. All had been febrile for three

weeks or longer before treatment was instituted. All had definite evidence of embolization, and 10 of the 11 had splenomegaly. Ten had repeatedly positive blood cultures for alpha streptococci, and 1 had repeatedly positive blood cultures of beta hemolytic streptococci. Summaries of our cases are presented in table 3.

Of our 11 cases, in 3 the result was a definite failure. The time intervals since completion of treatment in our 7 cases of probable cures in which the patients are living are: 1 case, eighteen months; 3 cases, twelve months; and 3 cases, eleven months. The remaining patient died on the last day of combined penicillin-heparin treatment. She had no evidence of active endocarditis, and it is possible that heparinization was a primary cause of death. Although this patient died, she was free of all evidence of active endocarditis at postmortem examination, and the cultures obtained at autopsy from the blood and the

Fig. 4.—Example of record followed for each patient.

heart valve were negative. Of the 11 patients, 7 are probably cured and are living, and 1 was rendered free of endocarditis but died as a result of cerebral hemorrhage. Two additional patients whose cultures were not positive have been rendered afebrile and asymptomatic since completion of their treatment.

DATA OBTAINED AT AUTOPSY IN AUTHORS' CASES

CASE 1 (A. G.).—Postmortem examination revealed chronic rheumatic mitral valvulitis with no definite vegetations (fig. 5), renal and splenic infarcts and cerebral hemorrhage (fig. 6) involving the left frontal and parietal lobes and originating from the left middle cerebral vessels. Heparinization may have played a primary role in this patient's death. No evidence of active subacute bacterial endocarditis was present at postmortem examination.

CASE 3 (C. M.).—Postmortem examination, performed by Dr. Pliny Allen, revealed moderate dilatation of all chambers of the heart, which was, however, maximal in the left auricle and ventricle. The myocardium was slightly soft

TABLE 3.—*Results of Treatment in Authors' Cases*

Patient	Race	Sex	Age, Yr.	Duration of Symptoms Prior to Rx	Etiology of Heart Disease	Valves Affected	Blood Cultures	Penicillin Route, Amount/24 Hr., Duration Rx	Heparin: Days Used; Reactions	Sulfadiazine, Amount and Duration of Rx	No. of Courses of Penicillin and Heparin and Sulfadiazine	Results and Months Since Completion of Treatment
1. A. G.	W	F	22	4½ wk.	Rheumatic	Mitral	Alpha strep.	200,000 units per 24 hr. I.V.; 13 days	13 days; 1 reactions	None during penicillin Rx	1	Died (figs. 5, 6). Cerebral hemorrhage; no evidence of subacute bacterial endocarditis
2. L. R.	W	M	47	4 wk.	Rheumatic	Mitral, aortic	B. hemolytic strep.	200,000 units per 24 hr. I.V.; 14 days	10 days; no reactions	None during penicillin Rx	2	Cure, 18 mo.; afebrile, asymptomatic
3. C. M.	C	M	27	8 wk.	Rheumatic	Mitral	Alpha strep.	200,000 units per 24 hr. I.V.; 16 days	14 days; 6 reactions	None during penicillin Rx	3	Died (figs. 7, 8). Uremia and congestive heart failure and subacute bacterial endocarditis
4. B. A.	W	F	18	7 wk.	Rheumatic	Mitral, aortic	Alpha strep.	200,000 units per 24 hr. I.V.; 16 days	9 days; 12 reactions (during 4 courses of Rx)	1 Gm. every 4 hr. day and night	4	Died. Uremia and congestive heart failure and subacute bacterial endocarditis
5. J. M.	C	F	20	1 mo.	Rheumatic	Mitral	Alpha strep.	200,000 units per 24 hr. I.V.; 17 days	13 days; no reactions	None during penicillin Rx	1	Cure, 12 mo. Afebrile, asymptomatic
6. E. Z.	C	F	25	3 mo.	Rheumatic	Mitral	Alpha strep.	144,000 units per 24 hr. I.M. (÷ doses every 2 hr.); 27 days	16 days; no reactions	1 Gm. every 4 hr. day and night	1	Died (figs. 9, 10). Congestive failure and subacute bacterial endocarditis

	Race	Sex	Age	Duration	Type	Valve	Blood culture	Penicillin	Sulfonamide	Other	No.	Result
7. V. L.	W	F	29	1 mo.	Rheumatic	Mitral, aortic	Alpha strep.	200,000 units per 24 hr. I.V.; 13 days	8 days; 8 reactions	None during penicillin Rx	2	Cure, 12 mo. Afebrile, asymptomatic
8. A. R.	W	F	24	4½ mo.	Rheumatic	Mitral	Alpha strep.	200,000 units per 24 hr. I.M.; 2 wk.; 100,000 units per 24 hr. I.M.; 2 wk.	None used	1 Gm. every 4 hr. day and night	1	Cure, 12 mo. Afebrile, asymptomatic
9. L. R.	C	M	19	3 wk.	Rheumatic	Mitral	Alpha strep.	144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 28 days	14 days; no reactions	1 Gm. every 4 hr. day and night	1	Cure, 11 mo. Afebrile, asymptomatic
10. I. L.	W	F	24	6 mo.	Rheumatic	Mitral	Alpha strep.	200,000 units per 24 hr. I.M.; (÷ doses every 3 hr.); 12 days	None	None	1	Cure,* 11 mo. Afebrile, asymptomatic
11. E. C.	C	M	23	4½ wk.	Congenital	Patent ductus arteriosus (fig. 11)	Alpha strep	144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 30 days	11 days; 4 reactions	1 Gm. every 4 hr. day and night	1	Cure, 11 mo. Afebrile, asymptomatic
12. E. P.	O	F	17	2 mo.	Poss. rheumatic	Pulmonary, mitral	Negative	144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 27 days	16 days; no reactions	1 Gm. every 4 hr. day and night	1	Cure, 9 mo.
13. D. P.	W	M	37	2 mo.	Rheumatic	Aortic, mitral	Negative	144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 27 days	17 days; 14 reactions	1 Gm. every 4 hr. day and night	1	Cure,† 6 mo.

* We have learned that this patient died 11 months after completion of treatment. However, her physician reported that no evidence of active subacute bacterial endocarditis was present.
† This patient has recently returned to the hospital and is apparently in the bacteria-free stage of subacute bacterial endocarditis.

and reddish brown. The endocardium of the right side of the heart was smooth and glistening, and the tricuspid and pulmonary valves weic delicate and competent and showed nothing of note. The endocardium of the left auricle was slightly

Fig. 5.—Chronic rheumatic mitral valvulitis in A. G. There were no definite vegetations

Fig. 6.—Cerebral hemorrhage involving the left frontal and parietal lobes (A G.).

thickened and milky with a single oval patch measuring 2.5 by 2 cm. on the posterior wall just above the posterior leaflet of the mitral valve. The base of this patch was rough and red, and the patch was continuous with vegetations along the line of closure of the posterior leaflet of the mitral valve. These vegetations measured approximately 0.7 by 0.4 by 0.3 cm, and were firm and gray inferiorly, merging imperceptibly into the reddened, shaggy patch on the auricular wall superiorly. The anterior leaflet of the mitral valve was thickened moderately and showed a few vegetations. Some of the chordae tendineae were thickened, shortened and fused, especially those of the posterior leaflet. The aortic valve showed a slight degree of adherence at the commissures, and just beneath the commissures, between the posterior and left anterior cusps, was a single, soft, yellow vegetation, 0 1 cm in diameter (fig. 7).

The final postmortem diagnosis was: (1) rheumatic heart disease with mitral and aortic valvulitis; (2) subacute bacterial endocarditis (Streptococcus viridans) involving the walls of the left auricle, mitral valve and aortic valve; (3) Strep.

Fig. 7.—Subacute bacterial endocarditis involving the walls of the left auricle of C. M.

viridans septicemia; (4) acute septic splenitis; (5) embolic glomerulonephritis with diffuse fibrous glomerulitis; (6) chronic passive congestion of the lung, spleen and liver; (7) pneumonia (rheumatic); (8) acute hepatitis; (9) portal cirrhosis of the liver (fig. 8); (10) ascites, and (11) chronic interstitial pancreatitis Blood cultures and culture of the valve produced growth of Strep viridans.

CASE 4 (B. A.).—Postmortem examination revealed: (1) adhesive pericarditis; (2) rheumatic valvulitis (healed); (3) subacute bacterial endocarditis involving the mitral valve; (4) cardiac hypertrophy and dilatation; (5) infarctions of the spleen and kidney; (6) bronchopneumonia and (7) passive congestion of the intestine with hemorrhage into the mesentery of the small intestine.

CASE 6 (E Z.).—At postmortem examination the heart weighed 395 Gm There were a few subepicardial petechiae. The chambers of both sides of the heart were considerably dilated. The valves of the right side of the heart and the

aortic valve showed nothing of note. The endocardium of the left auricle was slightly thickened, and over the posterior wall of the left auricle was a rounded patch measuring 5 by 4.5 cm., where the endocardium was completely covered by
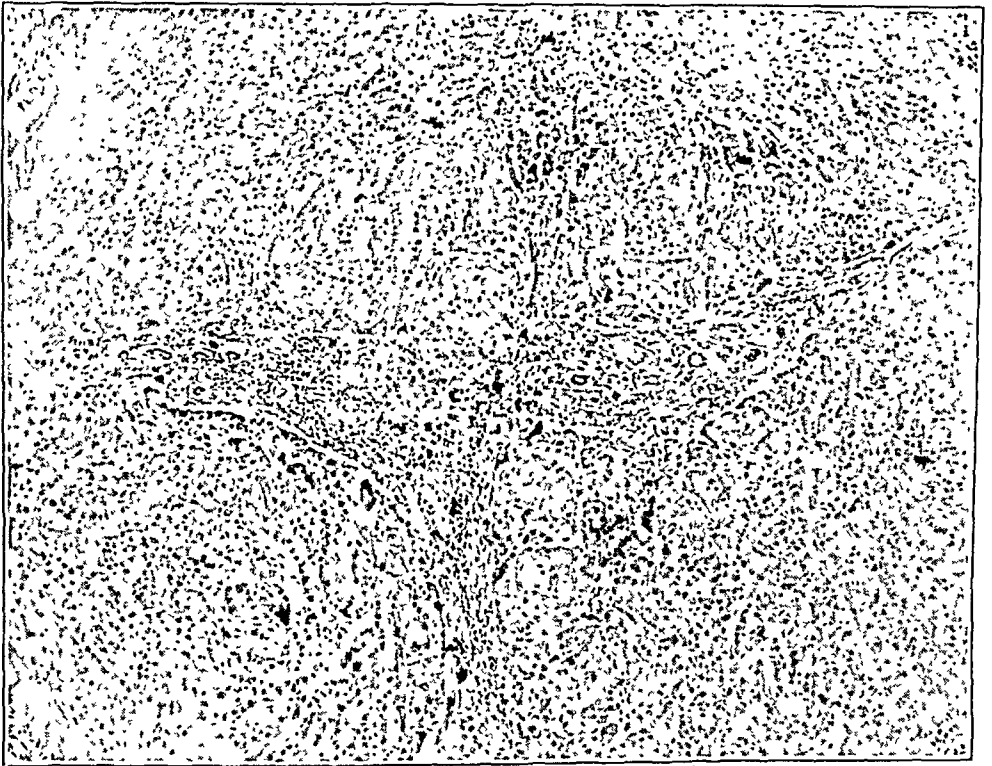
Fig. 8.—Portal cirrhosis (C. M.).
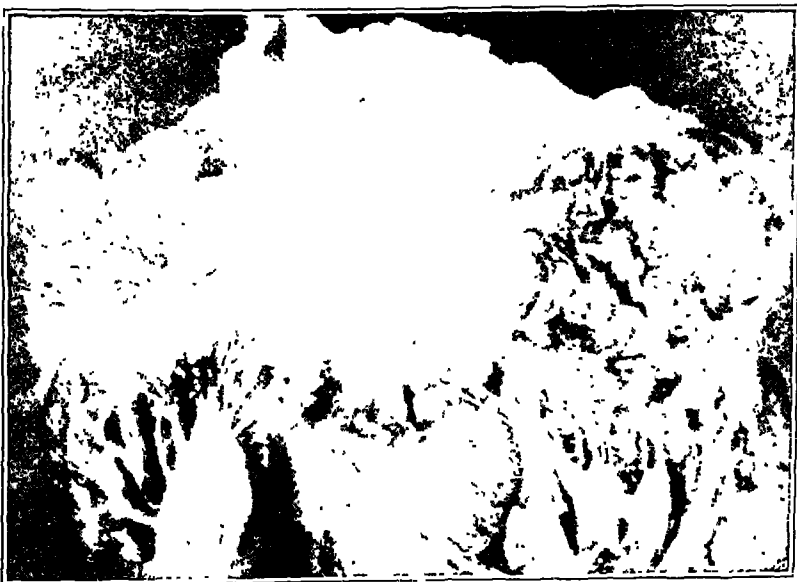
Fig. 9.—Subacute bacterial endocarditis involving the posterior wall of the left auricle and mitral valve of E. Z.

yellow-green, thick, soft, friable vegetations. The inferior edge of this patch extended onto the posterior leaflet of the mitral valve, involving it also in vegetations which extended down the chordae tendineae to the papillary muscles. Many

Fig. 10.—Mycotic aneurysm of the posterior medullary branch of the left middle cerebral artery of E. Z.

Fig. 11.—Injection of diodrast into patent ductus arteriosus of E. C.

chordae tendineae were thickened and 'fused, and one on the medial edge of the posterior leaflet of the mitral valve was ruptured at the junction with the valve at a site heavily involved in the vegetation. The entire line of closure of the valve showed numerous vegetations extending along the anterior and posterior leaflets (fig. 9).

The final postmortem diagnosis was: (1) rheumatic heart disease with mitral valvulitis, myocarditis and chronic pericarditis; (2) subacute bacterial endocarditis involving the posterior wall of the left auricle and mitral valve; (3) interstitial pneumonia; (4) cardiac dilatation and hypertrophy; (5) right hydrothorax; (6) hydropericardium; (7) ascites; (8) chronic passive congestion; (9) fatty metamorphosis of the liver; (10) multiple infarcts of the spleen, lungs and kidneys; (11) embolic glomerulonephritis; (12) cerebral embolus infarction; (13) generalized petechial hemorrhages and (14) mycotic aneurysm of the posterior medullary branch of the left middle cerebral artery (fig. 10).

Blood cultures at autopsy and culture from the heart valve yielded Strep. viridans.

COMMENT

Theoretic considerations and autopsy observations in 1 of our fatal cases have caused us to form the opinion that heparinization favors fragmentation of the vegetations, leading to embolism, and that large cerebral hemorrhages are due to bleeding into infarcted areas as a result of diminished coagulability of the blood.

According to Allen,[41] the vegetations typically consist of three zones: The inner zone, which forms the bulk of the lesion, consists of a mass of fibrin and blood cells, in which varying degrees of necrosis occur. Allen found strands and bits of elastic and collagenous fibers in this zone, and believes it is derived from an exudative and destructive lesion of the cusp. The middle zone, of varying thickness, is composed of bacteria. The outer zone, usually only a fraction of a millimeter thick, consists of a layer of fibrin derived from the blood stream.

The vegetation, unlike ordinary thrombi, grows by propagation of the inner zones, not of the thin outer layer. Emboli probably break off owing to fragmentation which begins in 'the inner, necrotic zone. Heparinization would not induce such fragmentation, but might prevent reformation of the outer fibrinous layer at the site of rupture and thus allow continued breakdown of the vegetation, even to the point of complete disintegration, which is what apparently happened in 1 of our cases.

The dangers attendant on the employment of heparin are the possible initiation of embolism, the bleeding which may occur around the infarcted areas owing to prolonged clotting time of the blood and reactions due to sensitivity to heparin. McLean and others [42] also con

41. Allen, A. C.: The Nature of the Vegetations of Bacterial Endocarditis, Arch. Path. **27**:661 (April) 1939.

42. McLean, J.; Meyer, B. B. M., and Griffith, J. M.: Heparin in Subacute Bacterial Endocarditis, J. A. M. A. **117**:1870 (Nov. 29) 1941.

sider the possibility of embolization being induced by the mechanical factors produced when excessive fluidity of the blood is caused by intravenous administration of heparin.

At present we advise heparinization only in those. cases in which the disease has failed to undergo remission with one course of penicillin therapy. In such a case we would hope that heparinization might cause disintegration of the vegetations, and pray that the fragments will not enter the cerebral vessels.

The final evaluation of the part heparin will play in the treatment of subacute bacterial endocarditis will not be made until comparable series of large numbers of cases with and without the use of heparin are reported.

The results with penicillin therapy indicate the first real advance that has been made toward the conquering of a disease which previously had a mortality close to 100 per cent. Penicillin is by far the most effective agent we have for the treatment of. subacute bacterial endocarditis. From the results available, it appears that endocarditis, in common with empyema and pneumococcus meningitis, will require prolonged administration of large doses of penicillin. At least 200,000 units a day for one month seems to be the optimal minimal dose in most cases. This dose should be increased if prompt remission is not induced. An occasional patient, as we demonstrated, succeeded in maintaining complete recovery after completion of two weeks of penicillin therapy. At present we believe that intramuscular administration at two hour intervals is the route of choice when therapy is to be continued so long.

Although various factors play a part in determining the final outcome of penicillin therapy, two main features determine its efficiency. The first factor is the extent of accessibility of the bacteriostatic and bactericidal action [43] of penicillin to the offending streptococci. This is determined in part by the size of the vegetation and the amount of fibrin and platelet barrier which is present on the vegetation. This in turn is dependent on the duration of the disease, those cases of over a few months' duration presenting more difficult opposition to the penetration of the vegetation by penicillin. The longer the endocarditis has been present, the more likely will be the possibility of permanent cardiac and renal damage. Even if the patient should recover from a long-standing endocarditis, his cardiac and renal status may be of such a low reserve as completely to incapacitate him or cause death. These are the reasons for the necessity of early diagnosis and early institution of treatment with adequate amounts of penicillin continued for a satisfactory interval.

43. Hobby, G. L.; Meyer, K., and Chaffee, E.: Observations on the Mechanism of Action of Penicillin, Proc. Soc. Exper. Biol. & Med. **50**:281, 1942.

After a patient recovers from an episode of subacute bacterial endocarditis, he should have a careful follow-up study and should be seen at least once every month for the first year. Foci of infection should be thoroughly investigated. Diseased tonsils, abscessed teeth and any other source of introduction of organisms into the blood stream should be eradicated. We advise that any dental or operative procedure be preceded and followed by the use of penicillin, as suggested by numerous authors.[44] It is well to keep in mind that minor manipulations of the teeth and gums may cause bacteremia. Okell and Elliott [45] found transient bacteremia following dental extractions in 75 per cent of patients with septic mouths, and in 34 per cent of patients without obvious dental infections.

SUMMARY

1. The recent literature on the therapy of subacute bacterial endo-
carditis is briefly summarized.

2. We have presented our method of treatment of subacute bacterial endocarditis. The value of heparin, its mode of administration and reactions to it are discussed. Details of administration of penicillin and our views on the combination of penicillin with heparin and sulfadiazine have been discussed.

3. Nine cases in which the patients were treated with penicillin, heparin and sulfadiazine, and 2 in which they were treated with penicillin alone are summarized. Of our 11 patients, 7 are considered probably cured; 1 died from a heparin reaction, although she was free of all evidence of endocarditis at postmortem examination; and 3 failed to recover. Two additional cases with negative cultures, in which subacute bacterial endocarditis was successfully treated with penicillin, heparin and sulfadiazine are presented.

44. Budnitz, E.; Nizel, A. E., and Berg, L.: Prophylactic Use of Sulfapyridine in Patients Susceptible to Subacute Bacterial Endocarditis Following Dental Surgical Procedures: Preliminary Report, J. Am. Dent. A. **29**:346, 1942. Northrop, P. M., and Crowley, M. C.: The Prophylactic Use of Sulfathiazole in Transient Bacteriemia Following Extraction of Teeth: A Preliminary Report, J. Oral Surg. **1**:19, 1943; Further Studies on the Effect of the Prophylactic Use of Sulfathiazole and Sulfamerazine on Bacteremia Following Extraction of Teeth, ibid. **2**:134, 1944. Schwartz, S. P., and Salman, I.: The Effects of Oral Surgery on the Course of Patients with Diseases of the Heart, Am. J. Orthodontics **28**:331, 1942.

45. Okell, C. C., and Elliott, S. D.: Bacteriemia and Oral Sepsis with Special Reference to the Etiology of Subacute Endocarditis, Lancet **2**:869, 1935.

STUDIES ON HYPERTENSION

VI. Effect of Lowering the Blood Pressures of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearances

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THE common therapeutic practice of attempting to lower the blood pressure of hypertensive patients makes it wise to determine whether such lowering of blood pressure may have any adverse influence. In view of the relationship of arterial pressure to renal filtration, the frequency with which hypertensive states are associated with pathologic glomerular changes and the associated abnormalities which might influence arteriolar renal blood flow, it seemed especially desirable to determine whether therapeutically induced significant falls in blood pressure would affect renal function.

This problem has been previously investigated by the urea clearance as the criterion of renal function. It was found [1] that there was a decrease in urea clearance during the period that the blood pressure of hypertensive patients was decreased by spinal anesthesia. In view of the admitted defects of urea clearance as a method of determining renal function, we have reinvestigated the problem with the more precise methods of inulin and diodrast clearances.

METHODS

Spinal anesthesia was induced by methods previously described.[2] Inulin clearances were studied with the one dose method of Alving and Miller,[3] and diodrast

1. Gregory, R.; Lindley, E. L., and Levine, H.: Studies on Hypertension: I. The Effect on the Renal Function of Decreasing the Blood Pressure of Patients with Hypertension, Texas Rep. Biol. & Med. 1:59-76, 1943.

2. Gregory, R.; Lindley, E. L., and Levine, H.: Studies on Hypertension: II. The Effect of Spinal Anesthesia on the Blood Pressure of Hypertensive Patients; Its Possible Bearing on the Pathogenesis of Essential Hypertension, Texas Rep. Biol. & Med. 1:167-206, 1943; footnote 1.

3. Alving, A. S., and Miller, B. F.: A Practical Method for the Measurement of Glomerular Filtration Rate (Inulin Clearance), Arch. Int. Med. 66:306-318 (Aug.) 1940.

clearances were determined according to the method of Goldring and Chasis.[4] The chemical determinations for inulin were made by Harrison's [5] modification of Alving, Rubin and Miller's method,[6] and the chemical estimations of diodrast were made according to the procedure employed by Alving, Flox and Pitesky.[7] Control clearance periods were run, and experimental clearance periods were run on a subsequent day—usually within three days after the control periods. Clearance periods were of approximately one hour's duration. It should be emphasized that the second hour of the experimental clearance periods served as a further control period, inasmuch as the blood pressure usually had risen to or toward the original levels.

RESULTS

Table 1 shows values for inulin and diodrast clearance and filtration fractions obtained from the study of 4 patients with normal blood pressures. The results are within the accepted range of normal values for inulin.[7] Although the values obtained for diodrast clearances are

TABLE 1.—*Inulin and Diodrast Clearances of Patients with Normal Blood Pressure*

Patient	Age	Blood Pressure	Inulin Clearance		Diodrast Clearance		Filtration Fraction		Diagnosis
			First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour	
P. P.	37	124/86	99	76	479	407	0.207	0.186	Nontoxic adenoma of thyroid gland
F. J.	67	150/84	106	..	336	332	0.312	.....	Chronic duodenal ulcer
B. B.	53	130/68	83	76	312	314	0.266	0.242	Infection of upper respiratory tract
M. S.	50	116/70	100	77	449	444	0.223	0.175	Pulmonary abscess

somewhat less than those noted by Goldring and Chasis,[8] they conform to the normal figures given by White, Findley and Edwards [9] and Chesley and Chesley.[10]

4. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, The Commonwealth Fund, 1944, p. 196.

5. Harrison, H. E.: A Modification of the Diphenylamine Method for Determination of Inulin, Proc. Soc. Exper. Biol. & Med. **49**:111-114, 1942.

6. Alving, A. S.; Rubin, J., and Miller, B. F.: A Direct Colorimetric Method for the Determination of Inulin in Blood and Urine, J. Biol. Chem. **127**:609-616, 1939.

7. Flox, J.; Pitesky, I., and Alving, A. S.: A Direct Photoelectric Colorimetric Method for the Determination of Diodrast and Iodides in Blood and Urine, J. Biol. Chem. **142**:147-157, 1942.

8. Goldring and Chasis,[4] p. 56.

9. White, H. L.; Findley, T., Jr., and Edwards, J. C.: Interpretation of Diodrast Clearances in Man, Proc. Soc. Exper. Biol. & Med. **43**:11-14, 1940.

10. Chesley, L. C., and Chesley, E.: The Diodrast Clearances and Renal Blood Flow in Normal Pregnant and Non-Pregnant Women, Am. J. Physiol. **127**:731-737, 1939.

Table 2 contains values for inulin and diodrast clearances of 12 patients with hypertension selected at random before, during and immediately following the effects of high spinal anesthesia. Ten of these patients had received clinical diagnoses of essential hypertension. Two of them (L. F. and H. B.) undoubtedly had chronic glomerulonephritis, as our records showed they had passed through a nephrotic stage prior to the chronic stages. Four of the 12 (C. B., D. S., W. L. and H. B.) had nonprotein nitrogen values of 121 to 381, 78, 45 and 79 mg. per hundred cubic centimeters, respectively. None of the patients had cardiac failure as decided by clinical means or by normal venous pressures and circulation times in most cases. Only 1 patient (E. P.) failed to show a fall in pressure. The remaining 11 had falls of systolic pressure of from 40 to 140 mm. of mercury and of diastolic pressure of from 20 to 80 mm. Seven of them (E. G., E. R., C. B., M. L., F. H., M. D. and W. L.) had falls to normotensive levels for thirty-six to one hundred and twenty minutes. One (L. F.) experienced a fall of blood pressure to normotensive levels for only five minutes. One patient (D. S.) had a significant fall of pressure from 230 systolic and 146 diastolic to a low of 180 systolic and 110 diastolic, with a continuation of a significant fall for ninety-six minutes. G. M. had a fall from 252 systolic and 130 diastolic to a low of 164 systolic and 110 diastolic; a significant fall of blood pressure was maintained, however, for only twenty minutes. The blood pressure of H. B. fell from 236 systolic and 150 diastolic to a low of 170 systolic and 90 diastolic; but the significant fall persisted for only fifteen minutes.

Further analysis of the data in table 2 demonstrates that a significant fall in inulin and diodrast clearances occurred in every instance in which the blood pressure fell significantly for as long as fifteen minutes. It can also be seen that the degree of decrease in the inulin and diodrast clearance is roughly proportional to the amount and duration of the fall in blood pressure.

That the decrease in clearance values is probably caused by the drop in blood pressure is evidenced by the following data: 1. The clearance values invariably rose to or toward the control levels during the second experimental hour, when the blood pressure had risen to or toward control levels. 2. In several patients, exemplified by M. D., in whom the blood pressure remained low for two hours, the inulin and diodrast clearances remained proportionally low. 3. In 1 patient (E. P.), in whom there was no fall in blood pressure but a slight unexplained rise and in whom sensory paralysis had reached the second interspace and there was complete motor paralysis of the lower extremities, there was no decrease in clearance values but a definite increase in these clearances.

TABLE 2.—*Effect on Inulin and Diodrast Clearances of Lowering Blood Pressures of Patients with Hypertension by Means of High Spinal Anesthesia*

Patient	Blood Pressure		Duration of Significant Lowering, Min.	Sensory Level	Inulin Clearance						Diodrast Clearance						Filtration Fraction			
					Control		Experimental		% Change		Control		Experimental		% Change		Control		Experimental	
	Initial	Lowest			First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour	First Hour	Second Hour
E. G.	230/122	108/ 72	120	3d I. S.	66	56	40	87	−25	+18	208	212	102	102	−81	−59	0.317	0.264	0.392	0.85
E. R.	220/128	102/ 72	56	2d I. S.	84	71	50	124	−40	+75	295	270	234	254	−21	− 6	0.285	0.263	0.213	0.488
C. B.*	228/140	110/ 80	85	3d rib	10	8	3	7	−72	−15	27	29	5	14	−82	−50	0.37	0.276	0.557	0.472
M. L.	270/170	130/ 90	66	2d I. S.	..	143	112	126	−22	−12	..	645	472	771	−27	+20	.....	0.222	0.237	0.164
D. S.†	230/146	180/110	96	4th I. S.	48	43	39	49	−19	−14	119	119	102	125	−14	+ 5	0.406	0.361	0.382	0.392
F. H.	150/ 90	110/ 70	46	3d rib	93	82	77	89	−17	+ 9	452	382	283	344	−37	−10	0.206	0.214	0.272	0.258
M. D.	190/100	120/ 70	36	2d I. S.	98	116	73	83	−26	−28	475	486	357	357	−25	−27	0.206	0.238	0.204	0.231
G. M.	252/130	164/110	20	2d I. S.	62	63	46	49	−26	−22	240	268	221	243	−10	− 9	0.252	0.235	0.208	0.202
W. L.‡	180/120	120/ 76	84	3d I. S.	41	37	8	32	−81	−14	136	130	27	169	−81	+30	0.301	0.285	0.297	0.189
E. P.	150/110	No fall	Rose to 170/154	2d I. S.	62	57	73	78	+18	+37	345	340	403	402	+17	+18	0.180	0.168	0.181	0.194
L. F.(N)	142/ 86	98/ 62	5	Clavicle	25	19	18	13	−28	−32	437	367	333	416	−24	+13	0.057	0.052	0.054	0.031
H. B.(N)§	230/150	170/ 90	15	Clavicle	13	13	6	8	−51	−38	64	64	19	39	−70	−39	0.199	0.203	0.33	0.212

(N) Chronic nephritis.
* Nonprotein nitrogen 121-381 mg. per hundred cubic centimeters.
† Nonprotein nitrogen 78 mg. per hundred cubic centimeters.
‡ Nonprotein nitrogen 45 mg. per hundred cubic centimeters.
§ Nonprotein nitrogen 79 mg. per hundred cubic centimeters.

The filtration fraction is elevated in most patients with essential hypertension during even the early stages.[11] This is usually interpreted to be due to a selective increase in vasomotor tonus of the efferent glomerular arteriole.

The filtration fractions in this study were found to be high in 6 of 12 patients. Five patients had normal fractions, and 1 had a severely reduced filtration fraction. In the latter instance (L. F.) the filtration fraction was reduced to 0.05, about 25 per cent of the normal value. This patient (L. F.) had chronic glomerulonephritis, with a nephrotic syndrome and a greatly reduced filtration rate with a normal effective renal plasma flow. The other patient with nephritis (H. B.) had a normal filtration fraction.

Theoretically, one might expect that high filtration fractions associated with essential hypertension would fall under high spinal anesthesia if there is a selective increase in vasomotor tone to the efferent glomerular arteriole. Analysis of our filtration fractions yielded no uniform trend. Of the 6 patients (E. G., E. R., C. B., D. S., G. M. and W. L.) who had a high filtration fraction, 2 (E. G. and C. B.) showed a significant (more than 0.02) rise in filtration fraction, 2 (E. R. and G. M.) had a significant fall and 2 (D. S. and W. L.) showed no significant change in filtration fraction during high spinal anesthesia and associated significant falls of blood pressures.

We are unable to explain the lack of uniformity in the effect of spinal anesthesia on filtration fractions. It may be explained by the variability of several factors, such as the drop in blood pressure, different degrees of organic change in the afferent or efferent arterioles and differences in the amount of glomerular damage.

Certain other pertinent features of·this study have been graphically presented in charts 1, 2 and 3. Chart 1 summarizes the results on patient F. H., who had normal inulin and diodrast clearances. The blood pressure fell under spinal anesthesia to normotensive levels for approximately forty-five minutes. During the first hour's observation the inulin and diodrast clearances fell significantly. During the second hour of the experimental period the blood pressure returned to its original hypertensive levels. During this hour the inulin clearance returned to the control level and the diodrast clearance moved toward but did not attain control levels.

Chart 2 illustrates the results on M. D., who had normal renal clearance values. High spinal anesthesia, however, caused a great fall in blood pressure for the entire hour of the first clearance period and for more than half of the second clearance period. There was a significant

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11. Goldring and Chasis,[4] p. 61.

decrease in inulin and diodrast clearances during the first period. These values remained essentially the same during the second clearance period because of the persistence of the fall in blood pressure well into the second clearance period.
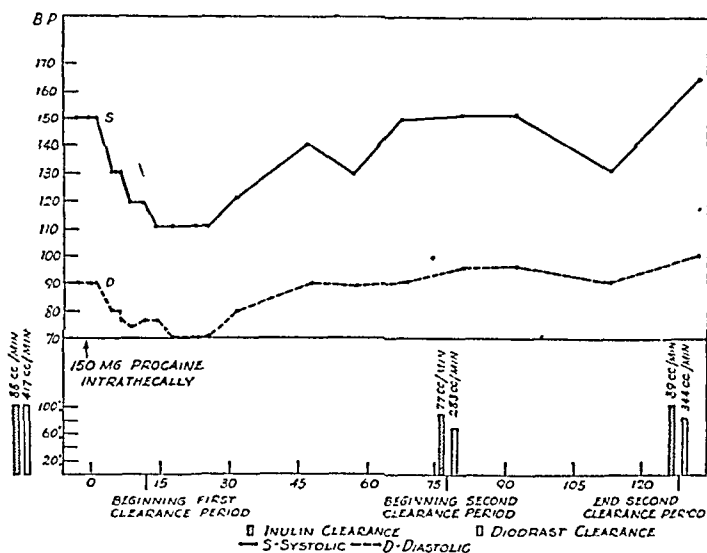
Chart 1 (patient F. H.).—Pattern of systolic and diastolic pressures during high spinal anesthesia in patient with normal inulin and diodrast clearances.
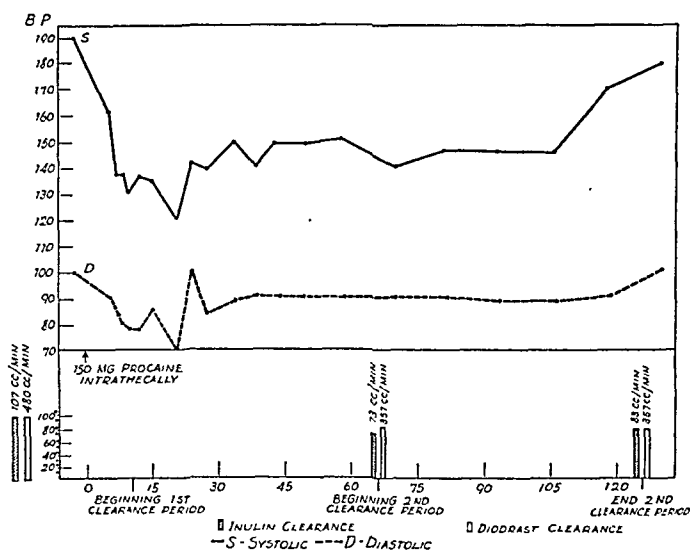
Chart 2 (patient M. D.).—Pattern of systolic and diastolic pressures during high spinal anesthesia in patient with normal renal clearance values.

Chart 3 graphically presents the data obtained from the study of W. L. This patient had great impairment of renal function, shown by low clearance values. During high spinal anesthesia the fall in blood pressure was great and the pressure remained at normotensive levels

during all of the first clearance period. Concurrently with this intensive drop in blood pressure, there was extreme depression of inulin and diodrast clearances. During the second clearance period the blood pressure rose rapidly toward the original level after the first twenty minutes of this period. The inulin clearances rose to the control level, and the diodrast clearance exceeded the control level during this period.

These figures graphically emphasize features which are shown in table 2, namely, that in hypertensive patients there is a close correlation between falls in blood pressure induced by high spinal anesthesia and inulin and diodrast clearances. This correlation occurs in patients with either normal or impaired renal function.

It is realized that the duration of the falls in blood pressure and the concomitant decreases in inulin and diodrast clearances are for short
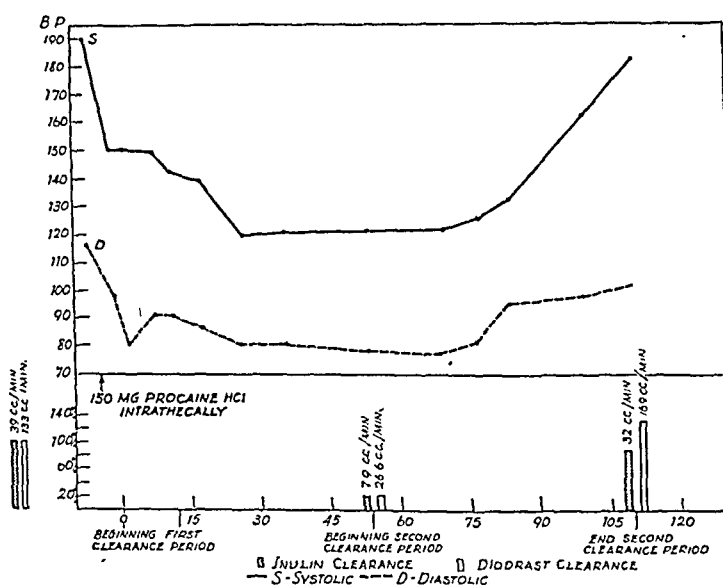
Chart 3 (patient W. L.).—Pattern of systolic and diastolic pressures during high spinal anesthesia in a patient with considerable impairment of renal function.

periods. The results of this study emphasize the necessity, however, for the study by precise methods of the effect on renal function of any therapeutic regimen which symptomatically lowers the blood pressure.

SUMMARY

The effect of lowering the blood pressure on renal function has been studied by inulin and diodrast clearances in 10 patients with essential hypertension and in 2 patients with chronic glomerulonephritis. The data have been presented in two tables and three graphs.

CONCLUSION

Fall in blood pressure induced by high spinal anesthesia to no lower than normotensive levels were associated with a decrease in inulin and

diodrast clearances in 10 patients with essential hypertension and in 2 . patients who had chronic glomerulonephritis.

It is believed that the fall in blood pressure is etiologically related to the decrease in renal function.

The decrease in renal function with the fall in blood pressure occurs in patients who have either normal or impaired renal function.

The results of this study necessitate a critical appraisal of the effect on renal function of any therapeutic effort which aims at symptomatic lowering of the blood pressure in patients with hypertension.

A ROENTGEN RAY AND CLINICAL STUDY OF PRIMARY TUBERCULOSIS

Vollmer Patch Test Made on Four Hundred and Sixty Patients; Positive Reactions Secured in One Hundred and Fifteen

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THERE is no uniformity of opinion concerning the fundamental biologic responses invoked in the human body when tubercle bacilli are introduced into it.

ALLERGY

There is abundant evidence that an allergic response is set up in the tissues of experimental animals by the introduction of tubercle bacilli. The first dose of tubercle bacilli injected into the skin of a guinea pig does not cause hyperemia. After sensitization the same dose will cause hyperemia. Long[1] has shown that a small dose of tubercle bacilli injected into the testis of a normal guinea pig has no immediate effect. However, if the animal has been previously sensitized, the same number of bacilli cause rapid degeneration of the testicle. It has been shown that leukocytes from normal animals are not harmed by contact with tuberculin, whereas leukocytes from tuberculous animals are damaged by similar contact.

Aronson[2] has shown that the growth of cultures of tissue from tuberculous guinea pigs is inhibited and their cells damaged by contact with tuberculin, whereas similar cultures from normal pigs are not thus affected by contact with tuberculin.

If tuberculoprotein is placed in the conjunctival sac of a sensitized guinea pig the destruction may be great enough to destroy vision. These and other evidences of the allergic response are summarized by Myers[3] in his monograph. This sensitizing process is said to vary with different species.

1. Long. E. R.: Tuberculous Reinfection and Tuberculin Reaction in Testicle of Tuberculous Guinea Pig, Am. Rev. Tuberc. 9:215-253 (May) 1924.

2. Aronson, J. D.; Zacks, D., and Poutas, J. J.: Comparative Sensitiveness of Pirquet and Intracutaneous Tuberculin Tests, Am. Rev. Tuberc. 27:465-473 (May) 1933. Aronson, J. D.: The Purified Protein Derivative, with Special Reference to Technique of Tuberculin Injections and Grading of Reactions, ibid. 30:727-732 (Dec.) 1934.

3. Myers, J. A., and others: Tuberculosis among Children and Young Adults, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1938.

IMMUNITY

Although it cannot be clearly demonstrated in the laboratory, there is a general belief that tubercle bacilli evoke some sort of immunologic process in the experimental animal and also in man. It has been shown that tubercle bacilli migrate more slowly from the point of injection to the internal structures in the sensitized animal than in the normal animal. Greater numbers of bacilli die out in the previously inoculated animal than in the normal animal. Koch[3] is said to have observed this phenomenon in part. Whether these two processes, i. e., allergy and immunity, exist as independent or as interdependent factors has not been determined.

In other parts of the globe millions of children have received injections of attenuated tubercle bacilli (BCG) with the idea of producing a protective immunity. There is no end of discussion about the value of this procedure.

The physician must decide which is the dominant one of these two factors in the spread and control of tuberculosis. Is it allergy, or is it immunity? Until recent years it has been an accepted belief that immunity is the dominant factor. The late eminent pathologist, H. G. Wells, used to say that the Lord's Prayer should be amended to read, "Give us this day our daily tubercle bacilli," thus emphasizing immunity to tuberculosis. On the other hand, in recent years Myers[3] and Stuart, who have devoted a great deal of time and energy to this problem, have presented much evidence, both laboratory and clinical, to indicate that allergy is the all-important factor in the spread and control of this disease. According to this conception, when tubercle bacilli are first introduced into the human body and produce the primary complex, this occurs uniformly without gross destruction of tissue and without discomfort to the host, in much the same way as the original introduction of ragweed pollen into the system occurs without symptoms.

Long and Seibert[4] have shown that the tubercle bacillus is composed of lipids, polysaccharides and an unstable water-soluble protein resembling albumin, and that sensitivity to tuberculin—and therefore the reaction to tuberculin tests—is due solely to this tuberculoprotein. The primary tuberculous infection sensitizes all the body tissues to tuberculoprotein; therefore, if a sufficient number of bacilli are introduced again into any part of the body an allergic response is invoked, char-

4. Long, E. R., and Seibert, F. B.: The Chemical Composition of the Active Principle of Tuberculin, Am. Rev. Tuberc. **13**:393-453 (May) 1926. Seibert, F. B.: The Chemical Composition of the Active Principle of Tuberculin: Isolation in Crystalline Form and Identification of Active Principle of Tuberculin, ibid. **17**:402-421 (April) 1928.

acterized by gross destruction of tissue—lung, kidney, bone, lymph node or epididymis. The relative importance of allergy and immunity in tuberculosis is debatable.

TUBERCULIN TESTS

Von Pirquet was the first to devise a tuberculin test which gained extensive recognition. He placed a little old tuberculin on the scarified skin. An indurated area appearing during the next forty-eight hours indicates sensitivity to tuberculoprotein. Later Mantoux modified the technic by injecting a small amount of old tuberculin intradermally. The Mantoux test detects a larger number·of reactors and therefore is considered superior to the von Pirquet test.

Seibert and Glenn[5] further modified the intracutaneous technic. Using their tuberculoprotein, which they designated "purified protein derivative," they injected a freshly prepared solution containing 0.00002 mg. of tuberculoprotein. This minute quantity is known as first test strength of purified protein derivative, and a test with it will be referred to in this study as P. P. D. test 1. As in·the Mantoux test, an indurated area of skin approximately 10 mm. or more in diameter appearing within forty-eight hours indicates sensitivity to tuberculoprotein and therefore to tuberculosis. If a person has a negative reaction to this test, he receives a second intracutaneous injection exactly two hundred and fifty times as great as the first. This amount is known as second test strength, and a test with it will be referred to in this study as P. P. D. test 2. If a person does not react to this test he is considered to be insensitive to tuberculin. In 1937, after years of investigation of tuberculosis by a committee on medical research of the National Tuberculosis Association, the managing director issued a statement indicating that purified protein derivative is distinctly superior to old tuberculin for intracutaneous tests. I therefore selected P. P. D. tests as a standard for testing the efficacy of the Vollmer patch test.[3]

Many attempts have been made to devise a satisfactory percutaneous test, or one in which the tuberculin is introduced into the deeper layers of the skin without the use of the needle. Tuberculin ointments proved unsatisfactory. Of the numerous patch tests, the one devised by Vollmer and Goldberger[6] and commercially prepared by Lederle Laboratories, Inc., appears to be the simplest and the most efficient. It consists of two pieces of absorbent material 1 cm. square which have

5. Seibert, F. B., and Glenn, J. T.: Tuberculin Purified Protein Derivative: Preparation and Analyses of a large Quantity for Standard, Am. Rev. Tuberc. **44**:9-25 (July) 1941. Seibert, F. B.: The Isolation and Properties of Purified Protein Derivative of Tuberculin, ibid. **30**:713-720 (Dec.) 1934.

6. Vollmer, H., and Goldberger, E. W.: New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019-1024 (Nov.) 1937.

previously been soaked in a suspension of old tuberculin and placed on an oblong strip of adhesive tape with a control piece between the two. After the skin has been thoroughly cleansed with acetone or ether to remove all fatty material, the patch is applied. It is removed after forty-eight hours and read after an additional forty-eight hours. When positive, the reaction appears as a sharply defined indurated reddened square, with lichenoid follicular elevations of the skin. If the reaction is strongly positive, there may be considerable induration of the skin spreading beyond the limits of the patch, followed by scaling and temporary pigmentation.

Vollmer and Goldberger first reported this technic in 1937 and stated that it was more sensitive than the von Pirquet test, with which they had compared it. Most experimenters agree with this statement. In subsequent reports,[7] using a stronger patch, Vollmer and Goldberger compared it with the P. P. D. tests and also with the Mantoux test with 0.1 mg. of old tuberculin. They reported almost 100 per cent agreement with these tests. The reports of other workers have been a little less favorable. In a series of 257 cases, Weiner and Neustadt[8] reported 95 per cent of the patients with positive reactions to the Mantoux also had positive reactions to the Vollmer Patch test. Hart[9] reported that patch tests detected 97 out of 100 Mantoux reactors. He used both the Vollmer patch and the Copenhagen patch. Court[10] reported 98 per cent agreement in 110 cases. Fineman and Bair[11] reported 97 per cent agreement in 330 cases. In both instances the Vollmer test was less sensitive than the Mantoux. Peck and Wegman[12] reported only 30 per cent agreement with the P.P.D. tests. This report is distinctly out of line with the others.

The purpose of this study is twofold: (1) to compare the sensitivity of the Vollmer patch with the purified protein derivative tests; and (2)—and this I regard as the more important—to make, record and correlate the clinical and roentgenologic observations on all positive reactors

7. Vollmer, H., and Goldberger, E. W.: Comparative Study of Tuberculin Patch Test and Mantoux Intracutaneous Test, Am. J. Dis. Child. **56:**584-586 (Sept.) 1938; Evaluation of the Tuberculin Patch Test (Vollmer-Lederle), ibid. **57:**1272-1277 (June) 1939.

8. Weiner, S. B., and Neustadt, A.: Tuberculin Patch Test: Comparison with Pirquet and Mantoux Tests, J. Pediat. **14:**752-754 (June) 1939.

9. Hart, F. D.: Tuberculin Patch Test in Children, Lancet **2:**609-610 (Sept. 10) 1938.

10. Court, S. D. M.: Comparative Study of Tuberculin "Patch Test" and the Intracutaneous Mantoux Test in Childhood, Brit. M. J. **1:**824-825 (April 22) 1939.

11. Fineman, A. H., and Bair, G.: Evaluation of Tuberculin Patch Test, Am. J. Dis. Child. **60:**631-634 (Sept.) 1940.

12. Peck, E. C., and Wegman, M. E.: Comparison of the Vollmer Tuberculin Patch Test with Purified Protein Derivative, J. Pediat. **15:**219-223 (Aug.) 1939.

over a long period. This should be valuable in appraising the relative importance of allergy and immunity in tuberculosis.

PROCEDURE

In the outpatient department of St. Luke's Hospital prior to 1941, my colleagues and I performed tuberculin tests on known contacts and on a few other children. During 1941 and 1942 every child over 1 year of age was tested with tuberculin as a matter of routine. On the appointed day, first test strength purified protein derivative was injected and the Vollmer patch applied. Two days later the child returned and the P. P. D. test 1 was read and the patch removed. In the event that P. P. D. test 1 elicited a negative or doubtful reaction second test strength P. P. D. test was given. The child again returned after two more days for reading of the patch and of P. P. D. test 2. If the results of the two tests did not agree or if the results were doubtful, the entire procedure was repeated as a check. To the 1941 and 1942 group were added those tested in previous years.

Therefore, this study does not indicate the percentage of reactors in our dispensary population. Every child tested is included in the summary except those who failed to go through with all the tests. The tests were completed on 460 children.

Of the total, exactly one fourth, or 115, reacted to at least one of the tests. These 115 were studied routinely as follows: They were questioned very carefully and diligently concerning exposure to tuberculosis. These children were brought back regularly every third or sixth month and in many cases oftener. At each visit they were weighed and measured, temperatures were taken, and physical examin--ations, including examinations of the chest, were made. Serial roentgenograms of the chest were made at regular intervals, usually once a year. Many chests were again given roentgenologic examination after two, three, four or six months, at the suggestion of the roentgenologist. These were cases that appeared to be changing more rapidly than others. More than half of these children have been under observation for five years; many of them ten years or longer.

Since all tuberculin tests are based on an allergic phenomenon, it follows necessarily that none is infallible. The possibility of false negative reactions and false positive reactions must always be borne in mind. For this reason it was considered necessary to keep each positive reactor under close clinical observation and to study him with serial roentgenograms.

The results of the observations on each of the 115 children with positive reactions to tuberculin were carefully tabulated and correlated. These observations include clinic identification number, race, sex, age, history of contact with communicable tuberculosis, results of tuberculin tests, observations from serial roentgenograms, red and white blood cell counts, estimations of hemoglobin, results of repeated examinations of

the chest and records of growth, weight and temperatures. The results of these studies are briefly set forth in the following paragraphs.

RESULTS

Racial Incidence.—The conception that certain races are more susceptible to tuberculosis than others has been challenged by Myers.[3] He stated his belief that the higher incidence of tuberculosis among Negroes, Mexicans and North American Indians is due to their poorer living conditions. I placed the Negroes and Mexicans in one group and compared the incidence to that in the white group. Among 293 dark-
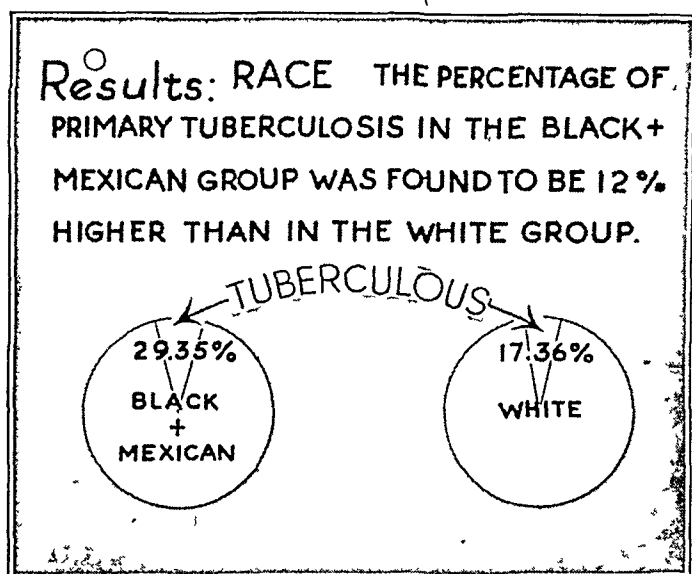
Figure 1.

skinned children, 86 had positive reactions to tuberculin and exhibited roentgenologic evidence of tuberculosis. In the white group, 29 out of a total of 167 gave the same evidence of primary tuberculosis. Thus the incidence of tuberculosis in the dark-skinned group was approximately 29 per cent as compared with 17 per cent in the white group (fig. 1). I believe that this difference of 12 per cent can be accounted for justly by the poorer living conditions of the former group.

Tuberculin Tests.—As stated earlier, 115 out of the whole group of 460 children reacted to at least one of the tuberculin tests. The Vollmer patch agreed with the purified protein derivative tests in 100 out of the 115 cases in which there was a reaction. Therefore the tests disagreed in 15 instances, or in 3 per cent of the entire series (fig. 2).

Of the 15 children concerning whom the Vollmer patch and the purified protein derivative tests did not agree, 14 had positive reactions to one of the purified protein derivative tests and negative reactions to

the Vollmer patch, whereas 1 child reacted to the patch and had an entirely negative reaction to both P. P. D. test 1 and P. P. D. test 2 (fig. 3). These facts indicate that neither test is infallible and also
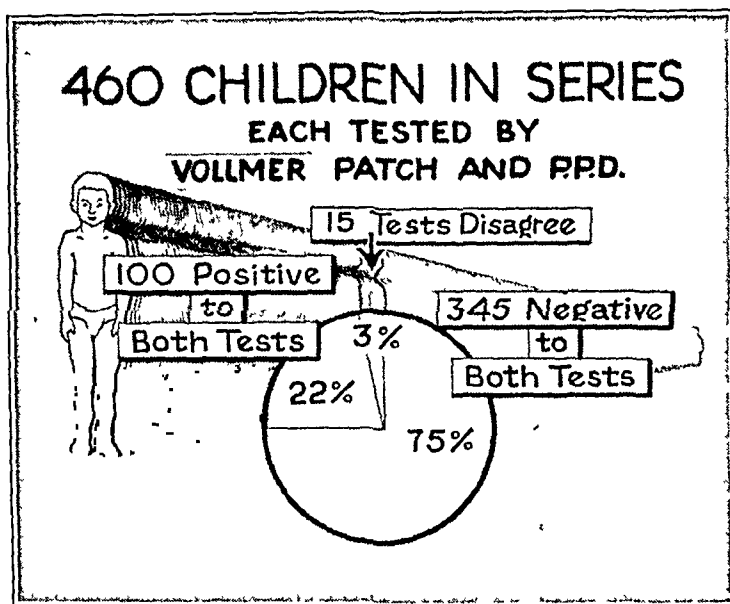
Figure 2.
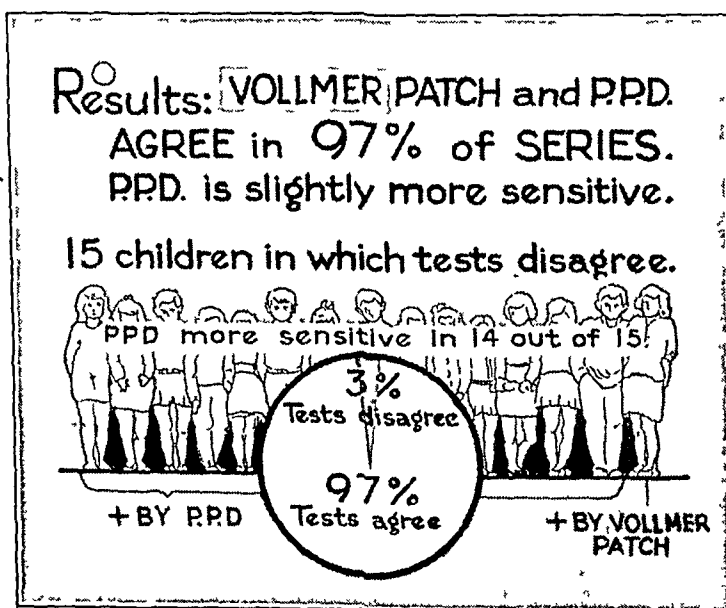
Figure 3

that the Vollmer patch test is slightly less sensitive than the purified, protein derivative tests.

Serial Roentgenograms.—Each of the 115 children whose reactions to tuberculin were positive has been examined at least once roentgeno-

logically. More than half of them have been examined by serial roent-
genograms over a period of five years, and some over a period of ten
years. The lesion of primary pulmonary tuberculosis appears first
peripherally. The usual location is the first, second or third intercostal
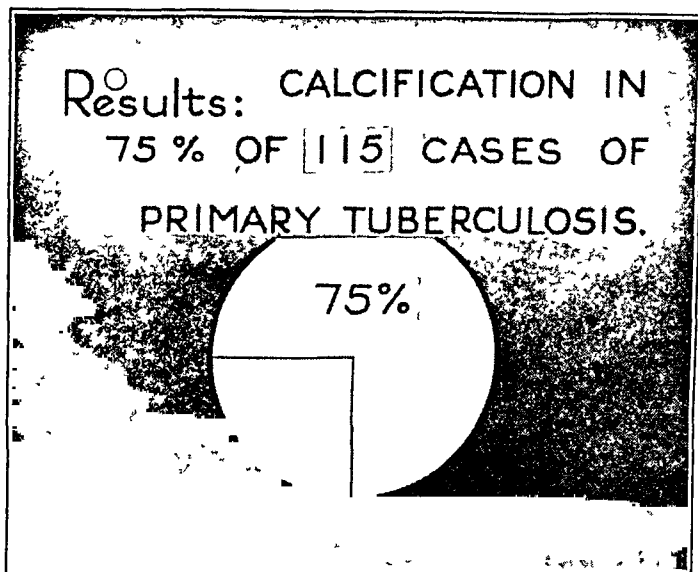
Figure 4.
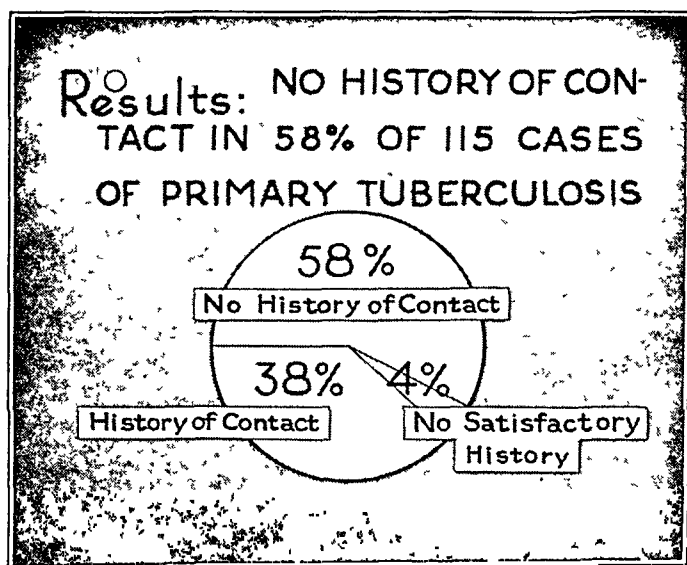
Figure 5.

space, on either the right or the left side. It is usually bilateral. It
may also be in the apex. This initial lesion is rather ephemeral and
rapidly hardens. At the same time the shadows of the hilar lymph
nodes enlarge. In a typical case, these slowly calcify. The end results

are calcified hilar nodes and linear peripheral markings. In some instances the peripheral lesion calcifies enough to register a dense shadow. This is a Ghon tubercle. In the present series this occurrence is decidedly the exception and not the rule. Calcification of hili is the rule and has already occurred in 84 cases, or 75 per cent of the series (fig. 4).

The majority of the patients dealt with in the present study had calcified glands at the first examination. In 18 calcification began while they were under observation. The interval between the first roentgenogram showing tissue change and the roentgenogram showing the appearance of calcium shadows varied from a few months to three years.
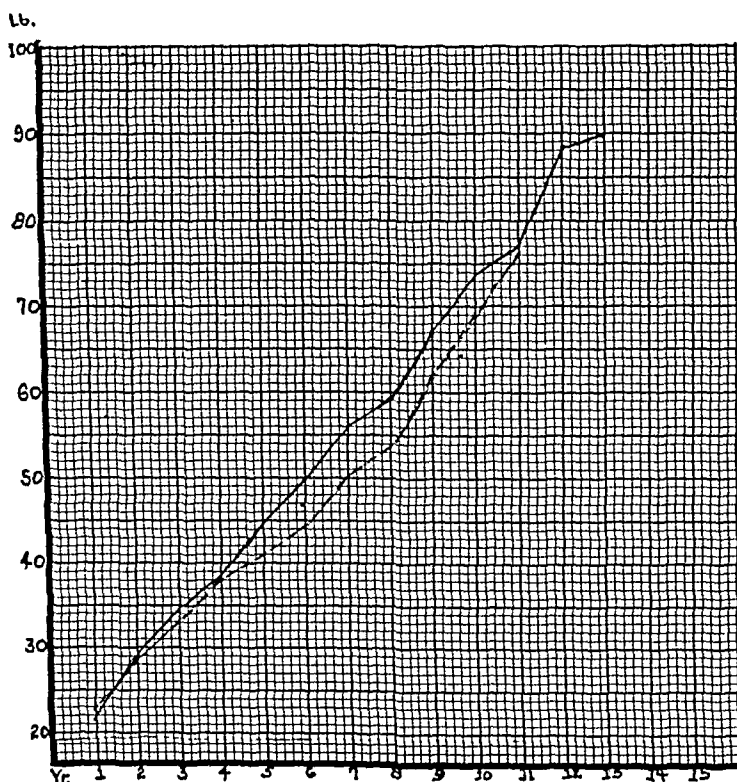
Fig. 6.—The solid line indicates the weights of boys whose reactions for tuberculosis are positive. The broken line indicates the weights of boys whose reactions are negative.

In the great majority of cases the lapse of time was between six months and two years. A very few remained without demonstrable calcification after three years. The roentgenograms in this series were read by Dr. E. L. Jenkinson and his associates.

There are no shadows specific for primary tuberculosis. The shadows caused by bronchitis or repeated respiratory infections are similar to those of primary tuberculosis. The roentgenologic observations must be correlated with the results of the test with tuberculin and the clinical history. In some instances a single roentgenogram is sufficient for this purpose; in others serial roentgenograms are necessary.

Incidence of Contact.—The history of each of the 115 patients was diligently explored and all clues followed. Yet a history of contact with communicable tuberculosis could be obtained in only 44 instances, or in 38 per cent of the series (fig. 5). Presumably the great majority of these children acquired the disease outside of their homes. This emphasizes the public health aspect of tuberculosis.
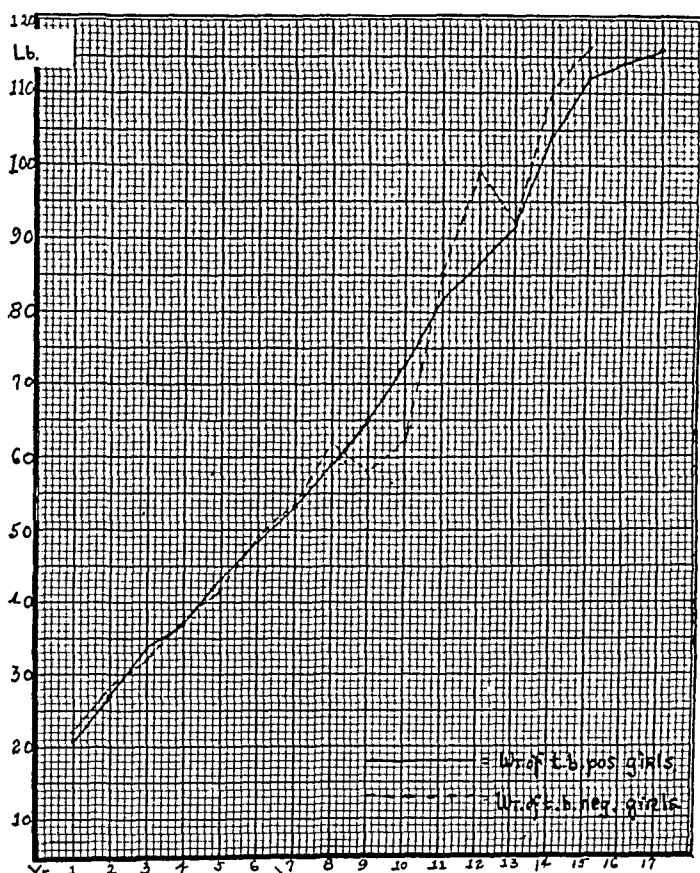
Fig. 7.—The solid line indicates the weights of girls whose reactions for tuberculosis are positive. The broken line indicates the weights of girls whose reactions are negative.

Clinical Data.—The general opinion among physicians appears to be that primary tuberculosis is a disease with mild clinical symptoms, such as a low grade fever with a generally poor state of health and perhaps some minimal physical signs in the chest. These opinions were not confirmed in this series, as the following data indicate:

Fever.—None of these children had a prolonged fever.

Blood.—Blood counts and estimations of hemoglobin were made for 110 of the 115 patients. The average red blood cell count was 4,100,000; the average white blood cell count, 7,500; the average hemoglobin content, 13.2 Gm. per hundred cubic centimeters (see the table).

Although there were no controls, these values are not significantly different from those of the average child encountered in the clinic.

Gain in Weight.—The boys and girls were divided into separate groups. The average gain in weight from 1 year of age until well into

Blood Counts in 115 Cases of Primary Tuberculosis

These counts are not significantly different from those of the average clinic child

Red cells	4,100,000
White cells	7,500
Hemoglobin	13.2 Gm.
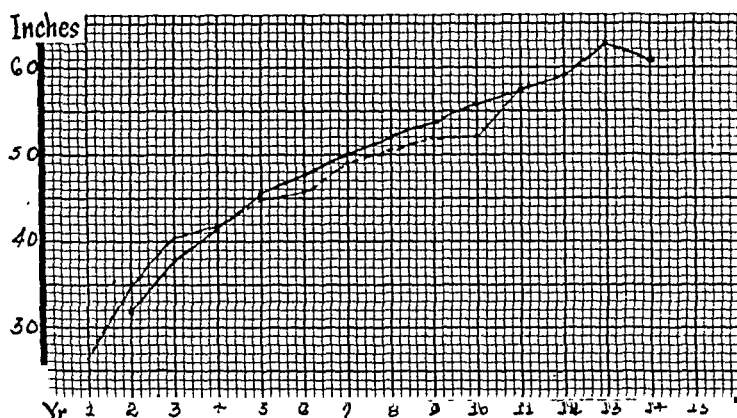
Fig. 8.—The solid line indicates the heights of boys whose reactions for tuberculosis are positive. The broken line indicates the heights of boys whose reactions are negative.
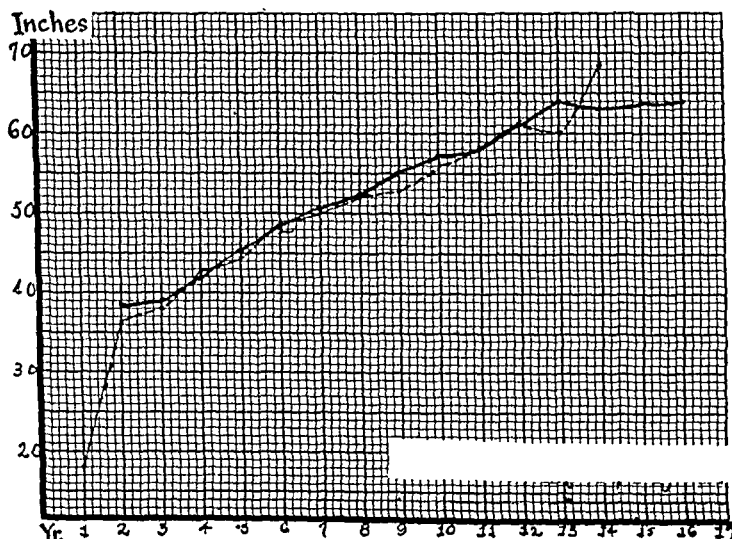
Fig. 9.—The solid line indicates the heights of girls whose reactions for tuberculosis are positive. The broken line indicates the heights of girls whose reactions are negative.

puberty was ascertained for each group and compared with that of a control group from the outpatient department. Graphs were made of the results. The gain in weight of the groups with primary tuberculosis

closely paralleled that of the controls. Figure 6 represents the boys' weight curves and figure 7 the girls' weight curves.

Gain in Height.—Similar graphs representing gain in height for both boys and girls and for controls were prepared. The growth in height of the tuberculous children closely paralleled that of the non-tuberculous (figs. 8 and 9).

Observations Concerning the Chest.—Frequently repeated auscultation and percussion of the chest of each of these 115 children failed to reveal any abnormality which could not be accounted for by some acute condition, such as an attack of asthma or of acute bronchitis.

SUMMARY AND CONCLUSIONS

The Vollmer patch test is somewhat less sensitive than the P. P. D. tests. It failed to detect the lesion in 14 of our series, 3 per cent of the entire group or 12 per cent of the positive reactors. It has the advantage of being painless, and it can be administered easily by an office or dispensary assistant. It seems fair to conclude that it is satisfactory for a large scale testing program or in other routine work where the time consumed often deters the physician from administering the P. P. D. or the Mantoux test. In this instance the percentage of error would be only 3. However, if diagnostic accuracy is desired, as in a case of suspected tuberculosis of bone, the P. P. D. tests should be used, because in that instance one would have twelve chances out of one hundred, or one out of eight, of missing the nature of the lesion.

As to the nature of primary tuberculosis of the lungs, I conclude that it is a subclinical disease. It cannot be detected by looking at a child or by making a physical examination or by making a blood count or by keeping a record of the child's weight or growth. History of exposure is the only satisfactory criterion by which it may be suspected. A tuberculin test is the only efficient means of detecting it. Serial roentgenograms are the most satisfactory means of following its course.

The most important question still remains. Will the incidence of destructive tuberculosis and the mortality be higher or lower in the 115 children with positive reactions than in the 345 children with negative reactions to tuberculin? If allergy is the dominant factor in destructive tuberculosis, a higher rate of morbidity and mortality is expected for the 115 positive reactors. On the other hand, if immunity is the dominant factor the morbidity and mortality rates should be lower for the positive reactors.

I expect to make a determined effort to enlarge these groups and to follow as many as possible through adolescence and beyond, in the hope that some additional knowledge may be obtained concerning this highly controversial subject.

ELECTROCARDIOGRAM IN TOXEMIAS OF PREGNANCY

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ELECTROCARDIOGRAPHIC patterns suggestive of an acute myocardial infarction of the anterior wall were found in 2 cases in which there was toxemia of pregnancy which resulted in cardiac failure. This unusual and apparently hitherto unreported observation raised the question of the significance of the electrocardiographic abnormalities in toxemia of pregnancy.

A survey of our electrocardiographic files disclosed 12 cases of toxemia of pregnancy without eclampsia. Each case had from one to five records consisting of three limb and two or three chest leads. Examination revealed that they fell into three groups. Group 1 consisted of the 2 cases already mentioned, which presented a classic picture of toxemia of pregnancy and resulted in acute left ventricular failure at the time of labor. Group 2 was made up of 4 cases which did not result in cardiac failure but in which nevertheless changes were manifested in the electrocardiogram. Group 3 consisted of 6 cases in which there was no evidence of cardiac failure and in which no electrocardiographic abnormalities were seen despite the presence of toxemia. Electrocardiograms for 5 normal pregnant women served as controls. None of the patients investigated in this study presented any previous history of cardiac disease.

ELECTROCARDIOGRAPHIC CHANGES IN TOXEMIA OF PREGNANCY WITH CARDIAC FAILURE

Two cases of electrocardiographic changes in toxemia of pregnancy with cardiac failure were found in our series, and the electrocardiograms are shown in figures 1 and 2.
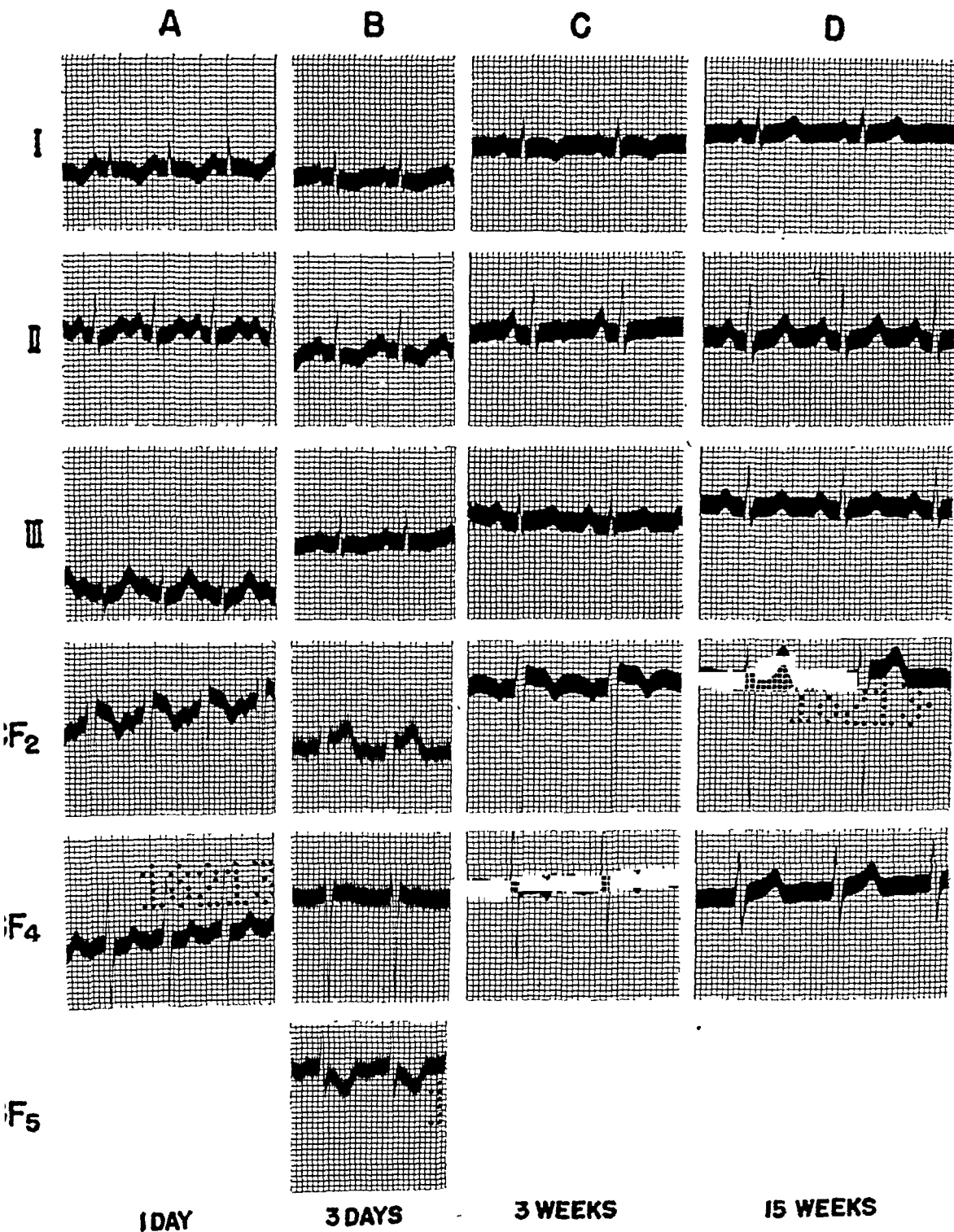
POSTPARTUM

Figure 1

(See legend on opposite page)

The electrocardiograms shown in figure 1 were obtained from a 31 year old white woman, bigravida, primipara, who had had no previous history of cardiac disease and in whom after nine uneventful lunar months of pregnancy a toxemia developed as shown by a hypertension of 170 systolic and 90 diastolic, by the presence of albumin (4 plus) in the urine and by considerable edema in her ankles. At term she went into labor spontaneously, at which time the classic signs and symptoms of acute left ventricular failure manifested themselves. Under a regimen of digitalis, oxygen and morphine sulfate, all signs of cardiac failure disappeared within one week. Four weeks post partum she was discharged from the hospital with a blood pressure of 120 systolic and 70 diastolic, without albuminuria and without edema.

The electrocardiograms shown in figure 2 were obtained from a 35 year old woman, trigravida, bipara, who had had no previous history of cardiac disease and in whom also there developed a classic toxemia of pregnancy. She entered the hospital during the ninth lunar month of pregnancy with a blood pressure of 174 systolic and 104 diastolic, albuminuria (2 plus) and pronounced edema of the lower extremities. During labor, which was induced, the patient experienced acute left ventricular failure. Treatment was similar to that outlined for the preceding patient. Except for a 700 cc. vaginal hemorrhage on the thirteenth postpartum day the patient improved, and she was discharged from the hospital·six weeks after entry with a blood pressure ranging from 150 systolic and 85 diastolic to 134 systolic and 80 diastolic, without edema and with an albuminuria of a trace to 1 plus.

Explanation of Figure 1

Electrocardiograms of a 31 year old white bigravida with toxemia of pregnancy and cardiac failure. *A*, taken one day post partum, shows a sinus tachycardia, low voltage and prolonged electrical systole. In lead I the T wave is inverted, peaked and symmetric; in leads II and III the S-T segments are depressed; in lead III the T wave is upright and peaked; in lead CF_2 the T wave is inverted and the R wave is small and in lead•CF_4 the S-T segment is depressed. *B*, taken two days after *A*, shows a slower rate and electrical systole of normal duration. In lead I the S-T segment is now depressed and the T wave is less inverted; in leads II and III the T waves are now inverted; in lead III the S-T segment is nondeviated; in lead CF_2 the T wave is upright; in lead CF_4 the S-T segment is nondeviated, the R wave is smaller, the S wave is deeper and the T wave is smaller, and in lead CF_6 the S-T segment is depressed and the T wave is inverted. *C*, taken fifteen days after *B*, shows a still slower rate. In leads II and III the P waves are taller, and in lead CF_2 the P wave is inverted. In the limb leads the S-T segments are nondeviated. In lead I the T wave is deeper; in lead II the T wave is tiny and diphasic, and in lead III the T wave is upright. The T wave is again inverted in lead CF_2 and is now also inverted in lead CF_4; the R wave is taller and the S wave is smaller in lead CF_4. *D*, taken twelve weeks after *C*, shows a normal contour; the low voltage and the S-T-T abnormalities have disappeared, and the R wave is of normal size in lead CF_2. It represents, therefore, complete restitution.
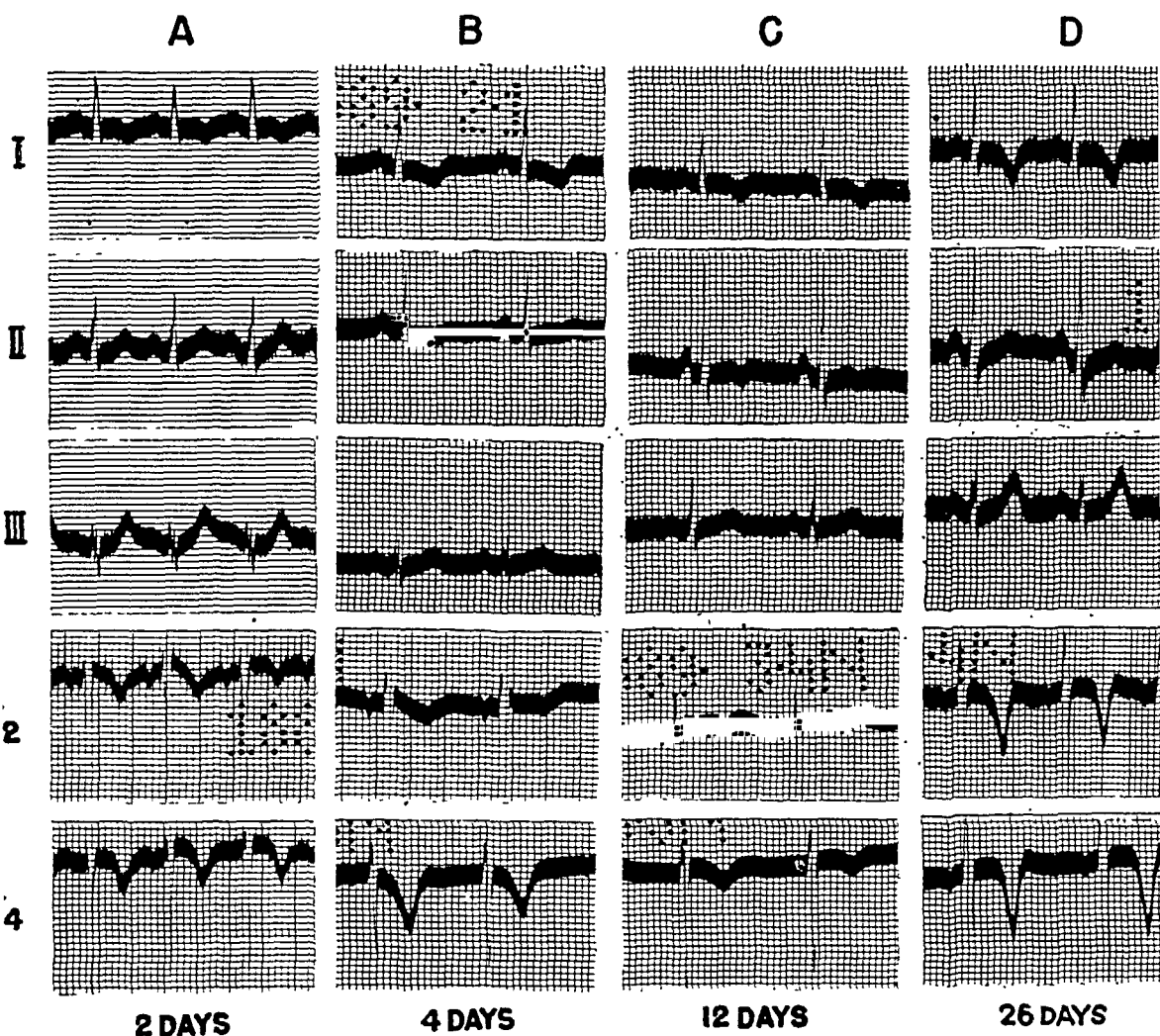
POSTPARTUM

Fig. 2.—Electrocardiograms of a 35 year old white trigravida with toxemia of pregnancy and cardiac failure. *A*, taken two days post partum, shows a sinus tachycardia, and low voltage, an inverted, peaked and symmetric T wave in lead I, a depressed S-T segment in leads II and III and an upright peaked symmetric T wave in lead III. No time lines are present in the limb leads. The R wave is small in leads CF_2 and CF_4, and the T wave is inverted in these leads. *B*, taken two days after *A*, shows a slower rate, and low voltage. In lead I the S-T segment is now depressed and the T wave is deeper; in lead II the T wave is diphasic, and in lead III the T wave is smaller. The QRS complex is M-shaped in lead CF_2; the R wave is taller and the S wave smaller in lead CF_4; the S-T segment is nondeviated in leads CF_2 and CF_4, and the T wave is deeper in lead CF_4 and smaller in lead CF_2. *C*, taken eight days after *B*, shows the R wave taller in leads II and III, the S-T segment nondeviated in the limb leads, and the T wave inverted in lead II. The R wave is taller in lead CF_2, the S wave is deeper in lead CF_4, and the T wave is less inverted in leads CF_2 and CF_4. In leads II and III the P wave is taller. *D*, taken two weeks after *C*, shows the R wave taller in lead I and smaller in lead III. The T wave is now deeply inverted, peaked and symmetric in lead I and upright, peaked and symmetric in lead III. The S-T segment is slightly depressed in the limb leads and the T wave is upright in lead II. The R wave is taller in leads CF_2 and CF_4, and the T wave is deeply inverted in these leads.

The electrocardiograms obtained from both of these patients are characterized chiefly by the waxing and waning of the symmetrically inverted T wave in leads I, CF_2 and CF_4, and of an upright symmetric T wave in lead III, the absence of any pronounced S-T deviation and the absence of changes in the QRS complex characteristic of myocardial infarction. One series shows complete restitution to normal within fifteen weeks; the other, unfortunately, could not be followed. These changes simulate those occasionally seen in acute nephritis.[1]

It is interesting that neither patient complained of pain in the chest at any time, although the former noted a sense of compression in her chest which accompanied the pronounced dyspnea at the time of the onset of the acute left ventricular failure. In 13 similar cases of toxemia of pregnancy reported in the literature[2] there was no mention of any complaints of precordial pain. Another interesting observation was that neither patient showed any lowering of the diastolic blood pressure at the time of the cardiac failure. The first patient had a 40 mm. drop of systolic pressure, which returned to its former level within twelve hours. In the second case no drop of the systolic pressure occurred.

These 2 patients, who without any previous history of heart disease experienced a toxemia of pregnancy and cardiac failure at the time of delivery, are not unusual. A review of the literature reveals similar cases.

Thus Gouley, McMillan and Bellet[2a] reported 3 such patients who experienced cardiac failure a short time following delivery. All 3 died, and at autopsy the histopathologic sections of the heart revealed disintegration of the myocardial fibers with lesser involvement of the nuclei. Hemorrhage into these areas was common. A moderate number of lymphocytes and macrophages, occasional neutrophils and eosinophils were present. The pathologic change was not confined to focal destruction. In many fields the structure of the muscles was intact, but the fibers showed definite degenerative changes. The coronary arteries were normal and patent throughout. Death occurred in 3 cases following pulmonary embolism which had its origin in thrombi adherent to the endocardial surface of degenerated cardiac muscle. No other proved source of embolism was found. Gouley and his

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1. Langendorf, R., and Pick, A.: Elektrokardiogramm bei akuter Nephritis, Acta med. Scandinav. **94**:1, 1938.

2. (a) Gouley, B. A.; McMillan, T. M., and Bellet, S.: Idiopathic Myocardial Degeneration Associated with Pregnancy and Especially the Puerperium, Am. J. M. Sc. **194**:185, 1937. (b) Teel, H. M.; Reid, D. E., and Hertig, A. T.: Cardiac Asthma and Acute Pulmonary Edema: Complications of Nonconvulsive Toxemia of Pregnancy, Surg., Gynec. & Obst. **64**:39, 1937. (c) Reid, D. E., and Teel, H. M.: Cardiac Asthma and Acute Pulmonary Edema Complicating Toxemias of Pregnancy: Further Observations, J. A. M. A. **113**:1628 (Oct. 28) 1939.

colleagues stated that the electrocardiograms (which were not illustrated) indicated that myocardial damage had occurred in all such patients, but that there was no clue to the cause. Inversion of the T waves was seen in the various limb leads, either singly or in combination, but it did not indicate myocardial infarction. No chest leads were taken in the cases in which autopsies were performed.

Teel, Reid and Hertig [2b] reported a case of a 38 year old octipara who gave no previous history of cardiac disease and in whom an acute toxemia had developed during her seventh month of pregnancy. She experienced an acute pulmonary edema and died shortly afterward. At autopsy the heart, which weighed 335 Gm., showed normal patent coronary arteries. The valves of the heart were normal, and no mural thrombi were found. Microscopic examination revealed pronounced edema of the stroma and occasional moderate-sized areas of the edematous stroma in which there was infiltration of polymorphonuclear and mononuclear leukocytes. Teel and his colleagues did not note any Aschoff bodies, necrosis or fatty degeneration of the myocardium.

Hull and Hafkesbring [3] described a case of a 16 year old Negro primipara who for four weeks prior to delivery presented the picture of extreme anasarca, dyspnea and gallop rhythm. After delivery she began to walk around, and the signs and symptoms of acute pulmonary edema became evident. Therapy was of no avail, and the patient died. At autopsy the heart was found to be enlarged but normal in weight (260 Gm.) The ventricular walls were of normal thickness, and the muscle was pale and friable. There were no valvular lesions. Microscopic examination revealed degeneration of the muscle fibers, interstitial hemorrhage and perivascular accumulation of lymphoid cells. Intense pulmonary edema was present. There was no anatomic evidence of preexisting hypertension. The electrocardiogram (not illustrated) in such cases of "toxic" postpartum cardiac disease was reported to be abnormal but was not characteristic. Low voltage was common and was ascribed to the extensive edema of the heart.

Hull and Hidden [4] illustrated electrocardiograms of the limb leads of patients who had postpartum cardiac failure and showed low or inverted T waves in leads I and II. Following improvement of 1 of these patients the T waves became upright.

In all the preceding cases postmortem examination revealed that the coronary arteries were normal and unobstructed. The pathologic

3. Hull, E., and Hafkesbring, E.: "Toxic" Post Partal Heart Failure, New Orleans M. & S. J. **89**:550, 1937.

4. Hull, E., and Hidden, E.: Post Partal Heart Failure, South. M. J. **31**: 265, 1938.

observations with respect to these hearts were always those of focal myocardial necrosis, edema or infiltration. The few electrocardiograms of limb leads which were obtained for these patients showed occasional inversions of T waves in leads I and II, and a few had low voltage. In the present 2 cases electrocardiograms (consisting of leads I, II, III, CF_2 and CF_4) showed the evolution of a pattern which might readily be interpreted as that of an atypical acute myocardial infarction of the anterior wall. In view of the pathologic observations in the similar cases reported by others, we believe that these electrocardiographic patterns were produced by focal myocardial necrosis, infiltration or edema rather than by a myocardial infarction secondary to occlusion of a coronary artery. Although occlusion of a coronary artery has been described in young persons, the occurrence in a young woman without any history of antecedent cardiac disease would be most unusual. It would appear that the ultimate prognosis in patients who recover from cardiac failure in toxemia of pregnancy is better than that following coronary disease, and that the electrocardiographic changes are based on focal myocardial necrosis, edema and infiltration rather than on occlusion of a coronary artery and massive myocardial infarction. A correct interpretation of the electrocardiographic pattern in these cases is therefore of practical value.

The changes found in the electrocardiograms obtained for our patients who experienced cardiac failure simulate rather closely those occasionally seen in acute nephritis.[1] This is significant in view of the fact that the pathologic cardiac changes in acute nephritis, while different from those in toxemias of pregnancy (in that they result from vascular damage) may also include edema with occasional inflammatory and degenerative changes of the cardiac muscle and its serous membranes.[5] The electrocardiographic changes found in both conditions are an expression of damage to the myocardium. It is possible that in some cases the damage may not be demonstrable histologically and may yet be sufficient to alter the electrocardiogram. When an electrocardiogram showing this pattern is obtained, the differential diagnosis is to be made by clinical investigation and correlation. Neither of our patients gave any evidence of having nephritis.

An interesting question is that of the cause of the cardiac failure. It is well known that in toxemia of pregnancy the heart is pumping against a tremendous load which consists of (1) an increased resistance in the systemic circuit with its consequent elevated blood pressure, (2) an increased volume of circulating blood and (3) generalized edema which, it must be remembered, is present in the lungs in the form of

5. Baehr, G.: The Nature of Glomerulonephritis, Bull. New York Acad. Med. **14**:53, 1938.

an interstitial edema and which gives rise to a pulmonary hypertension with its consequent strain on the right side of the heart. We believe that the focal myocardial necrosis, edema and infiltration are the essential factors which lead to the myocardial weakening and consequently may act as a precipitating mechanism in the cardiac failure.

Many ·of the cases reported by others resulted in cardiac failure in a few days to weeks following delivery. One of our patients with toxemia who did not experience cardiac failure is interesting in this respect since her electrocardiogram did not show any abnormalities until two days post partum. We believe that this might be an indication that the evidence of the damage to the myocardium may be present for some time after the emptying of the uterus. The continuation of damage to the myocardium in the early postpartum period might conceivably be responsible for the postpartum failure. This is compatible with the well known fact that toxemia may become more severe at this time. Dexter and Weiss [6] published an electrocardiogram of a hypertensive patient who experienced cardiac failure about one week before labor was induced. The electrocardiogram showed nothing abnormal at that time, but nine days postpartum inversions of T waves in leads I and IV_F were seen. Except for a less inverted T wave in lead I there was no change seen in the electrocardiogram taken nine and one-half weeks post partum. They suggest that these changes may have some bearing on certain cases of obscure postpartum failure.

ELECTROCARDIOGRAPHIC CHANGES IN TOXEMIA OF PREGNANCY WITHOUT CARDIAC FAILURE

Only 4 out of 10 cases of toxemia of pregnancy in which cardiac failure did not develop showed electrocardiographic abnormalities, and none of these were as pronounced as those in our 2 cases in which cardiac failure developed. In none of these cases were patterns present resembling an atypical acute infarction of the anterior wall or acute nephritis. Three of these 4 cases are illustrated in figures 3, 4 and 5.

The electrocardiograms shown in figure 3 were obtained from a 25 year old primigravida who during the last month of her pregnancy experienced a severe toxemia as indicated by a blood pressure of 220 systolic and 140 diastolic, generalized edema, blurring of vision and albuminuria. For two days following low cervical cesarean section the blood pressure maintained itself at 178 systolic and 130 diastolic to 155 systolic and 105 diastolic. Within a week the blood pressure returned to its level before pregnancy of 118 systolic and 88 diastolic. Except for

6. Dexter, L., and Weiss, S.: Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, Little, Brown & Company, 1941, p. 218.

a mild cystitis, the postpartum course was uneventful, and the patient was discharged sixteen days following delivery without edema; her urine gave a reaction of 1 plus for albumin, and her blood pressure

A **B** **C** **D** **E**

1 MONTH **1 DAY** **2 DAYS** **1 WEEK** **2 WEEKS**

A N T E P A R T U M **P O S T P A R T U M**
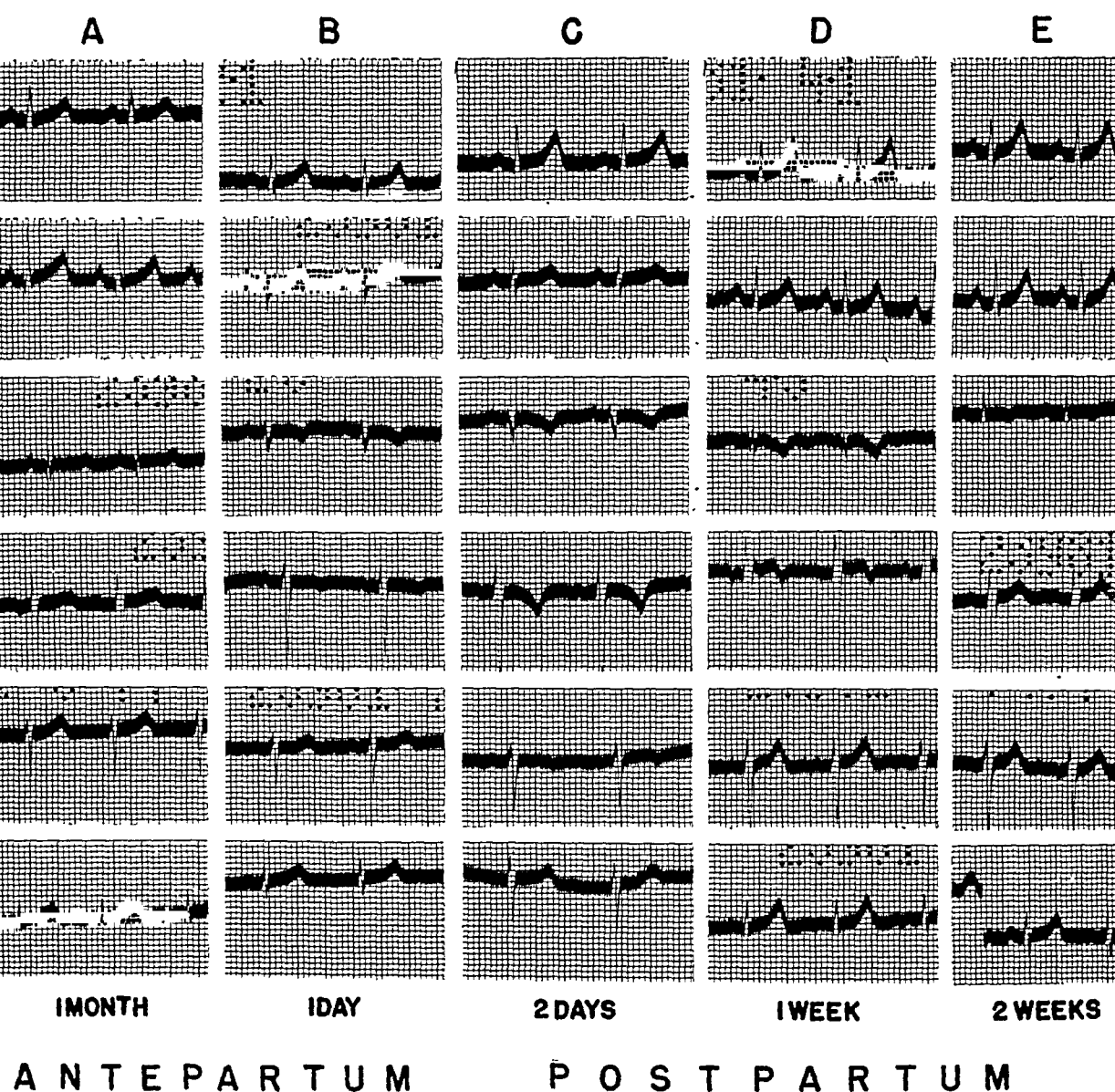
Fig. 3.—Electrocardiograms of a 25 year old Negro primigravida with toxemia of pregnancy but without cardiac failure. *A*, taken a month ante partum, shows a normal record with left axis shift. *B*, taken one day ante partum, shows low voltage. The R wave is smaller in leads I and II. A small S wave appears in lead I and a deep S wave in leads II and III; the T wave has become inverted in leads III and CF_2, and the R wave is smaller in lead CF_2. *C*, taken two days post partum, shows the R wave taller in leads I and II, the S wave absent in lead I and smaller in lead II, the T wave taller and peaked in lead I, deeper in leads III and CF_2 and small and inverted in CF_4, and the S wave deeper in CF_5. *D*, taken five days after *C*, shows the T wave taller in leads I and II, the R wave taller in lead II, the S wave absent in lead II, the T wave deeper in lead III, the R wave taller in lead CF_2, the S wave absent in lead CF_5 and the T wave diphasic in lead CF_2, upright in lead CF_4 and taller in lead CF_5. *E*, taken one week after *D*, differs only in minor details from *A* and therefore represents complete restitution.

was normal. This is an example of a woman who experienced a severe toxemia of pregnancy without subsequently having cardiac failure; however, electrocardiographic changes occurred two days following delivery.

The electrocardiograms shown in figure 4 were obtained from a 34 year old Negro septigravida, sextipara, who showed very mild symptoms of toxemia and who had pronounced fluctuations in blood pressure. A single reading recorded in the fourth month was 150 systolic and 80
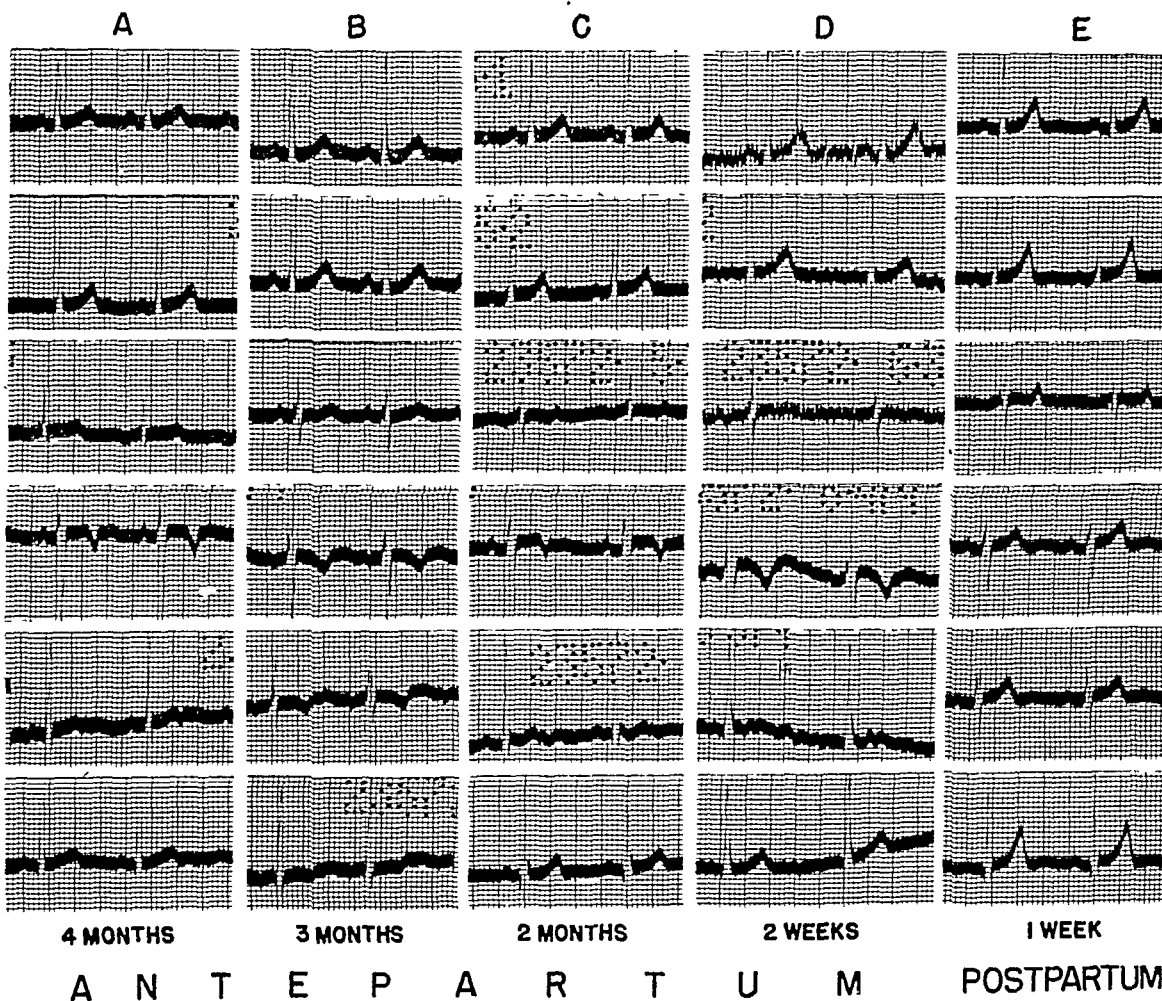
Fig. 4.—Electrocardiograms of a 34 year old Negro septigravida with mild toxemia of pregnancy but without cardiac failure. *A,* taken four months ante partum, shows as its only abnormalities an inverted T wave in lead CF₂ and a diphasic or notched T wave in lead CF₄. *B,* taken one month later, shows an S wave in lead III, a T wave that is broader and inverted in lead CF₂, inverted in lead CF₄ and diphasic in lead CF₅, an S wave that is smaller in lead CF₂ and more noticeable in lead CF₄ and an R wave that is smaller in lead CF₄. *C,* taken one month later, has reverted practically to the configuration in *A.* *D,* taken two weeks ante partum, shows a deeper T wave in lead CF₂ and a smaller R wave in this lead. (There is an extracardiac oscillatory artefact in this record.) *E,* taken one week post partum, shows a normal record with left axis shift, the abnormalities of the T wave in previous records being absent.

diastolic; during a two week period of observation at the hospital in the sixth month the blood pressure ranged from 190 systolic and 110 diastolic to 120 systolic and 80 diastolic; similar fluctuations were observed during the last two weeks before delivery, with readings ranging from 210 systolic and 110 diastolic to 120 systolic and 70 diastolic. After delivery the blood pressure was from 150 to 180 systolic and from 70 to 90 diastolic. We hesitated to ascribe the electrocardiographic changes found in this case to the mild toxemia of pregnancy. However, their disappearance after delivery together with the drop in blood pressure seem to justify the inclusion of this case as one of toxemia of pregnancy.

The electrocardiograms shown in figure 5 illustrate an instance of a very mild toxemia of pregnancy in a patient who did not experience cardiac failure. These records were obtained from a 16 year old Negro primigravida in whom during the last trimester of her pregnancy there began to develop a mild toxemia. She entered the hospital at term with a blood pressure of 145 systolic and 94 diastolic; her urine gave a reaction of from 1 to 3 plus for albumin, and there was a slight edema of the ankles. During the first three days following an uneventful spontaneous delivery her blood pressure ranged from 150 systolic and 110 diastolic to 142 systolic and 85 diastolic. By the tenth postpartum day no albuminuria or edema was present, and the blood pressure had returned to its level before pregnancy of 116 systolic and 80 diastolic.

The fourth patient with abnormalities in the electrocardiogram had a moderately severe toxemia and showed a transitory first degree auriculoventricular block (P-R interval of 0.22 second) in a record taken six days following delivery. Other records taken nine and five days ante partum, as well as three weeks post partum, showed the P-R interval ranging between 0.14 and 0.20 second. Except for the transitory first degree auriculoventricular block, there were no electrocardiographic abnormalities.

Abnormalities in the electrocardiogram do not occur in all cases of toxemia of pregnancy. Our electrocardiographic files contain six lead records of 6 patients with varying degrees of toxemia in none of whom were electrocardiographic abnormalities found. None of these women experienced cardiac failure.

THE ELECTROCARDIOGRAM IN NORMAL PREGNANCY

It is not possible to state that all cases of toxemia of pregnancy in which cardiac insufficiency develops do show electrocardiographic abnormalities. Our own 2 cases did, and those reported in the literature apparently also did. Furthermore, it is not possible to state that all abnormalities seen in cases of toxemia of pregnancy are due to the
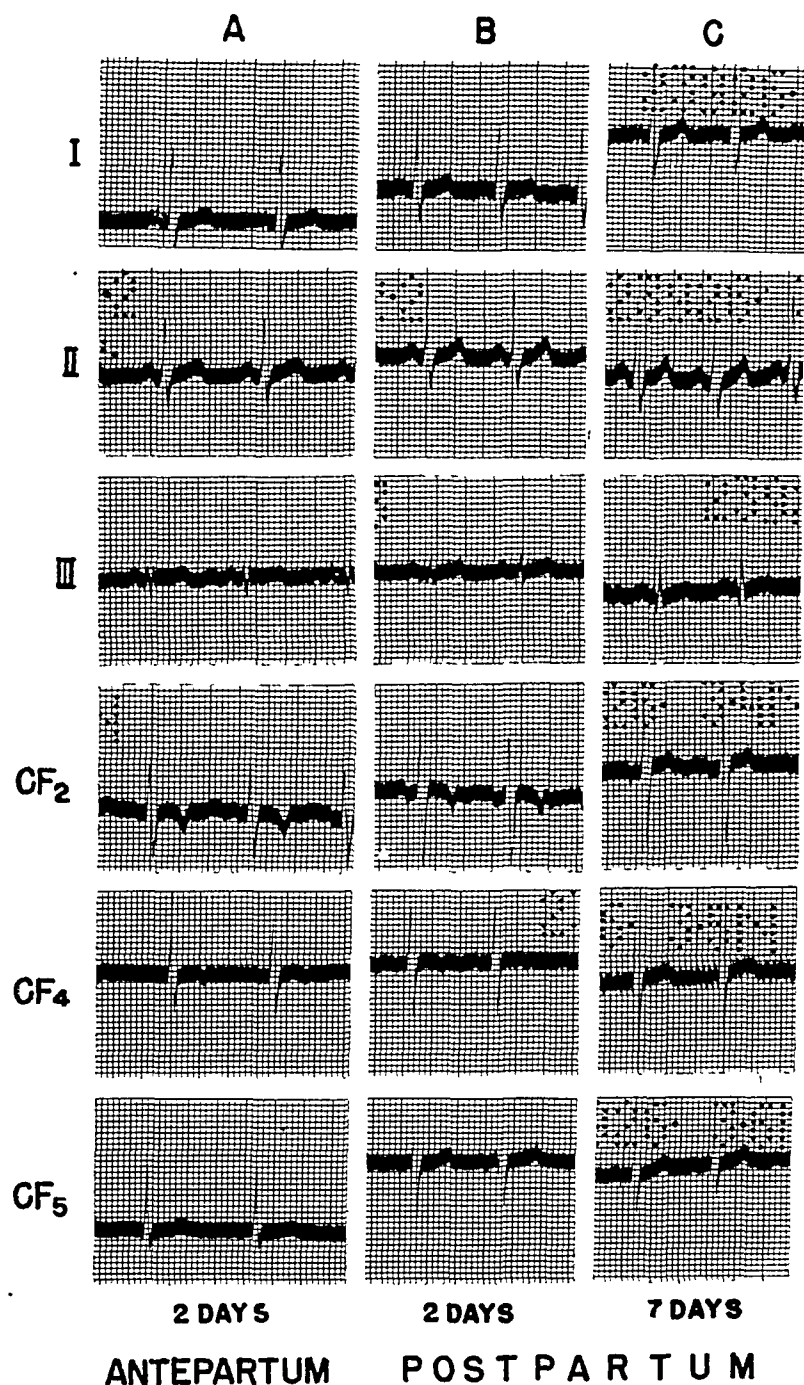
Fig. 5.—Electrocardiograms of a 16 year old Negro primigravida with mild toxemia of pregnancy but without cardiac failure. *A,* taken two days ante partum, shows normal limb leads, but the T wave is inverted in leads CF₂ and CF₄. *B,* taken two days post partum, shows a faster rate and a deeper S wave in leads I, II and CF₅, but otherwise *B* is similar to *A.* *C,* taken five days after *B,* shows the S wave deeper in leads I and II, the QRS complex in lead III upright and small, and the T wave upright in all leads. The inversions of the T wave in previous records are those associated with pregnancy.

toxemia. It is known that left axis shift, a prominent Q and a deep inversion of T waves in lead III develop in normal pregnancy.[7]

In our own series electrocardiograms were available for 5 normal women during the last month of their pregnancy. Except for the expected axis shift due to the altered position of the heart, no abnormalities were found. One record, however, is of possible significance in connection with the inversions of the T wave found in the cases of toxemia. This electrocardiogram is shown in figure 6 and was obtained for a 17 year old Negro girl who had a perfectly normal pregnancy and delivery. It shows a transitory inversion of the T wave in lead CF_2. This finding suggests that such inversions of the T wave in the chest leads may be normal occurrences in pregnancy.

Thus, in 1 of our 7 patients with toxemia and also in 1 of our 5 normal pregnant women inversion of the T wave occurred in leads CF_2 and CF_4. The inversions of the T wave in these leads were seen in the last month of pregnancy and persisted two days post partum. The T wave reverted to its normal upright form one week post partum. Since the uterus empties and the diaphragm·descends when delivery takes place, the change in the T wave after the second postpartum day eliminated the position of the heart as the sole factor in the causation of the inversions of the T wave. Dilatation of the heart secondary to the plethora which occurs in the last trimester of pregnancy and resolves slowly in the postpartum period may be the important factor. The role of the hormonal imbalance associated with pregnancy is not understood. It is interesting that the patient from whom the electrocardiogram illustrated in figure 5 was obtained, a 16 year old patient with a mild toxemia, had a blood pressure of 145 systolic and 94 diastolic when the inversion of the T wave was present in leads CF_2 and CF_4. One week later, when the blood pressure returned to a normal of 116 systolic and 80 diastolic, these T waves became upright. In the record taken one week post partum the S wave in lead I and the R wave in lead III had become larger, which indicates that an axis shift to the right had occurred.

The frequency of this inversion of the T wave in leads CF_2 and CF_4 in our small series is of the same order as that found by Thomson, Cohen and Hamilton,[7a] who used a chest lead which corresponds most closely

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7. (a) Thomson, K. J.; Cohen, M. E., and Hamilton, B. E.: Studies on the Circulation in Pregnancy: V. Lead Five of the Electrocardiogram in Pregnancy, Including Normal, Cardiac and Toxemic Women, Am. J. M. Sc. **196**:819, 1938. (b) Carr, F. B.; Hamilton, B. E., and Palmer, R. S.: The Significance of Large Q in Lead III of the Electrocardiogram During Pregnancy, Am. Heart J. **8**:519, 1933.

with lead CF_3 (the chest electrode was placed in the fourth interspace 5 cm. to the left of the midsternal line). They found that 7.7 per cent of normal pregnant women had an inverted T wave in this lead which reverted to an upright T wave some time following delivery. The post-partum electrocardiogram from a normal patient which they illustrated
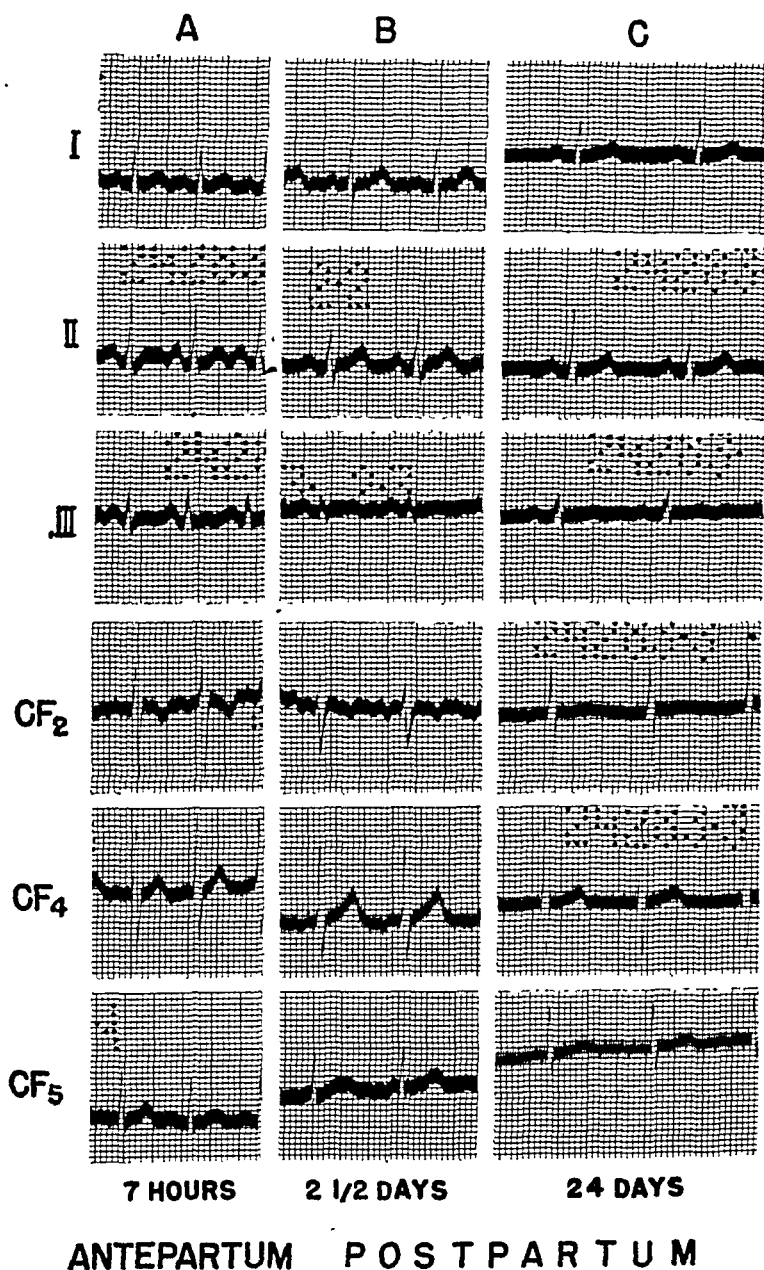
Fig. 6.—Electrocardiograms of a 17 year old Negro primigravida with a normal pregnancy. *A*, taken seven hours ante partum, shows a sinus tachycardia and an inversion of the T wave in lead CF_2. *B*, taken two and one-half days post partum, shows a slower rate and a T wave taller in leads I and II, less inverted in lead CF_2 and taller in lead CF_4; also a smaller R in CF_2, *C*, taken three weeks after *B*, shows a normal record with sinus rhythm and left axis shift; the changes in the T wave therefore are associated with pregnancy.

was taken six weeks after delivery. No statement was made as to how soon after delivery this reversion occurs.

SUMMARY

This study has indicated that abnormalities in the electrocardiogram in the toxemias of pregnancy are of two sorts, namely: (1) changes which occur with equal frequency in normal pregnancy and are therefore not related to the toxemia of pregnancy and (2) changes which do not occur in normal pregnancy and are therefore related to the toxemia.

At times the electrocardiographic changes are pronounced in toxemias of pregnancy, especially when heart failure develops. In such cases the pattern may closely resemble that seen in acute nephritis and may simulate an atypical pattern of acute infarction of the anterior wall.

The possible causes of these electrocardiographic abnormalities are discussed, and the practical significance of their evaluation is presented.

CONCLUSIONS

1. Patients with toxemia of pregnancy who experience cardiac failure show electrocardiographic abnormalities. Some of those who do not experience cardiac failure also show changes.

2. Focal myocardial necrosis, edema and infiltration secondary to toxemia of pregnancy may give an electrocardiographic picture which simulates that of acute nephritis or of an atypical acute myocardial infarction of the anterior wall. The myocardial involvement, as shown by changes in the T wave, may continue after delivery and is a possible factor in postpartum cardiac failure.

3. Inversion of the T wave in leads CF_2 and CF_4 occurring during the last trimester of pregnancy and reverting to its normal upright form within one week following delivery is possibly a result of dilatation of the heart. This occurs in a small percentage of normal and toxemic patients.

4. Transient first degree auriculoventricular block may occur (1 case is described which occurred in the postpartum period of a patient with toxemia of pregnancy).

5. A better ultimate prognosis may be made for a patient who recovers from cardiac failure secondary to toxemia of pregnancy as contrasted with the prognosis for a patient who recovers from a coronary occlusion with myocardial infarction. A correct interpretation of the electrocardiogram is important.

PROTHROMBIN LEVEL OF PERIPHERAL BLOOD AND STERNAL MARROW

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DESPITE the tremendous strides made in recent years in the understanding of the properties of prothrombin, its metabolic cycle remains a matter of conjecture. As far as is known, the liver is the site of production of prothrombin, and the precursor of thrombin is liberated into the circulating blood continuously and in excess. Of the fate and possible additional functions of prothrombin practically nothing is known. The manner in which vitamin K and dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) exert their respective influences on the prothrombin–elaborating system likewise remains obscure.

The evidence to prove that the liver is the major, if not the sole, locus for the synthesis of prothrombin is as yet neither complete nor conclusive. The conception is based on the demonstration that hepatocellular damage, artificially induced or occurring clinically, is accompanied with prothrombinopenia. Which of the components of the liver, the hepatic parenchymatous cells or the elements of the reticuloendothelial system encompassed by this most versatile organ, performs the function remains an unanswered question.

In a quest for evidence in substantiation or negation of these premises we undertook to determine whether a relationship could be established in respect to the production of prothrombin between reticuloendothelial activity and function presumably of the liver. This was accomplished by an indirect approach, namely, by a comparison of the prothrombin clotting time of plasmas obtained simultaneously from the peripheral venous blood and from the sternal bone marrow.

Forty-seven subjects were studied. They were all patients suffering with chronic disorders, their diagnoses varying from the common cardiovascular diseases and arthritides to the rarities of coarctation of the aorta and ochronosis. All adult age groups were represented, and the two sexes were equally divided.

An aspiration of sternal marrow and a venipuncture were made in each case, within a few minutes of each other. On 1 (subject 10) two such operations were done, one before and the other while he was under the influence of dicoumarin, the total comparisons therefore numbering 48. During each venipuncture, 4.5 cc. of blood was drawn into a syringe containing 0.5 cc. of tenth-molar sodium oxalate solution and the two were thoroughly admixed. After the needle was in the sternal marrow space 4.5 cc. of material was similarly aspirated into a syringe containing 0.5 cc. of the sodium oxalate solution. The aspirated material was found to be a composite of sternal marrow, a small amount of fatty substances and blood. This was well evidenced by differential cell counts and the thin supernatant layer of lipid material. These specimens were promptly centrifuged, clear plasma pipetted off and the estimation of prothrombin time made. All estimations were made in duplicate.

The method used for estimation of the prothrombin time was described in a previous publication of this series.[1] It included estimation of the prothrombin time of both whole and diluted (12.5 per cent) plasma. A thromboplastic agent of standardized activity prepared from desiccated fresh rabbit lung was used.

Comparative measurement of the prothrombin time was made on 28 patients receiving no medication. The data obtained in these cases are presented in table 1. There are no significant differences in the figures for whole plasma, and only 2 show differences in excess of five seconds in the prothrombin time of diluted (12.5 per cent) plasma.

The method of selecting a means to determine what constitutes a significant difference is worthy of discussion. The prothrombin times of the diluted plasma are much greater than those of the unmodified plasma and are subject to frequent and pronounced variations in patients with a disease, though in normal persons these values remain remarkably constant. Thus, the meaningful figures in these studies are the differences between the prothrombin time of plasma and of marrow of each subject rather than the variation between a given figure and the average of the group. It would lend additional support if the values were considered not only from the standpoint of the absolute figure but also in relation to the total time. Thus, we consider the minimum significant differences in the presence of normal dilute plasma prothrombin time (forty seconds) to be four seconds, which in relation to the total time is 10 per cent, while in the presence of prothrombinopenia the minimum significant difference becomes greater, depending on the extent of prolongation of the prothrombin time, and at least 10 per cent of the absolute value of the latter. For example, a difference of less than twenty seconds in a prothrombin time of two hundred seconds for dilute plasma would be considered not significant. The same principle is to be applied to differences in prothrombin time of unmodified plasma, except that the values are restricted to a range too narrow to reveal fine differences.

The average difference just described corresponds most closely to the statistical mean deviation, and we have adopted twice the relationship of the average difference to the average total time as the percentage of minimum significant difference.

RESULTS

Table 1 reveals the following salient features: The averages for plasma and marrow approximate each other remarkably in both the

1. Shapiro, S.; Sherwin, B.; Redish, M., and Campbell, H. A.: Prothrombin Estimation: Procedure and Clinical Interpretations. Proc. Soc. Exper. Biol. & Med. **50:**85, 1942.

whole and the diluted plasma. The averages of the differences in both phases are very small, and the differences are about equally divided between plasma greater and less than marrow, leading us to conclude that solely chance factors predominated in determining the quantity and direction of these small variations.

TABLE 1.—*Data for Twenty-Eight Subjects Who Received No Medications Known to Alter Prothrombin Levels*

Subject No.	Whole *				Dilute *			
	Plasma, Sec.	Marrow, Sec.	Differ-ence, Sec.	Plasma>Marrow— Plasma<Marrow+	Plasma, Sec.	Marrow, Sec.	Differ-ence, Sec.	Plasma>Marrow— Plasma<Marrow+
1	13.6	12.6	−1.0	=	41.0	47.0	+6.0	<
2	13.3	14.7	+1.4	=	34.5	36.2	+1.7	=
3	13.8	13.6	−0.2	=	44.4	41.4	−3.0	=
4	14.4	14.6	+0.2	=	44.2	46.4	+2.2	=
5	12.2	11.6	−0.6	=	33.2	31.2	−2.0	=
6	15.2	15.5	+0.3	=	45.2	50.6	+5.4	=
7	13.4	13.4	0.0	=	31.6	33.8	+2.2	=
8	17.2	16.8	−0.4	=	62.2	63.0	+0.8	=
9	12.4	11.4	−1.0	=	43.0	38.2	−4.8	=
10	15.4	13.0	−2.4	>	51.4	49.4	−2.0	=
11	13.4	15.0	+1.6	<	44.6	45.1	+0.5	=
12	12.6	12.9	+0.3	=	40.0	38.4	−1.6	=
13	15.0	16.7	+1.7	<	46.0	44.0	−2.0	=
14	14.9	13.9	−1.0	=	34.6	37.7	+3.1	=
15	12.2	12.9	+0.7	=	28.8	32.1	+3.3	=
16	13.2	14.1	.+0.9	=	35.1	37.7	+2.6	=
17	12.1	12.1	' 0.0	=	34.0	40.0	+6.0	<
18	13.8	14.0	+0.2	=	48.1	43.8	−4.3	=
19	12.7	12.1	−0.6	=	39.5	34.3	−5.2	>
20	13.6	11.8	−1.8	>	40.0	43.1	+3.1	=
21	14.6	13.8	−0.8	=	51.8	53.4	+1.6	=
22	14.8	15.4	+0.6	=	36.7	37.4	+0.7	=
23	13.8	13.2	−0.6	=	37.1	35.9	−1.2	=
24	14.6	13.9	−0.7	=	36.7	41.3	−4.6	=
25	14.9	15.2	+0.3	=	36.5	37.4	−0.1	=
26	16.6	17.1	+0.5	=	73.2	69.3	−3.9	=
27	13.3	13.6	+0.3	=	59.8	55.6	−4.2	=
28	16.4	15.2	−1.2	=	59.5	55.1	−4.4	=
Average	14.0	13.9	0.76		43.2	43.5	2.95	

M>P, 14 subjects, average 0.64 sec.   M>P, 15 subjects, average 2.88 sec.
M<P, 14 subjects, average 0.88 sec.   M<P, 13 subjects, average 3.0 sec.

* Note that the averages for plasma and marrow approximate each other remarkably in both the whole and the diluted plasma.

Table 2 is a frequency distribution of the data of table 1 and shows a fair parallelism of concentration and distribution of figures for plasma and marrow in both phases. The curves formed by charting the fig-ures in each column are akin to curves of normal distribution, skewed somewhat to the right, as might be expected since there is more oppor-tunity for a random scatter above the usual figures than below. The mean, medium and mode as well as mean deviation, standard deviation and probable error were all computed and charted. All these char-acteristics for both plasma and marrow lie in close proximity. The

mean, medium and mode have the usual relationship to each other found in most curves of normal distribution.

The foregoing facts tend to confirm rather definitely our impression that the character and amount of any deviations and discrepancies in these measurements are more than adequately attributable to fortuitous circumstances, such as the inevitable small differences in any experimental method using physical measurement.

Having thus demonstrated that there is no significant difference in the prothrombin level of peripheral blood and of bone marrow, we might logically progress one step further and conclude that the reticulo-

TABLE 2.—*Frequency Distribution* *

Group in Seconds	Number of Readings in Group		Group in Seconds	Number of Readings in Group	
	Whole Plasma	Whole Marrow		Dilute Plasma	Dilute Marrow
11.0-11.9	0	3	28-30.9	1	0
12.0-12.9	6	5	31-33.9	2	3
13.0-13.9	10	8	34-36.9	6	3
14.0-14.9	6	4	37-39.9	3	6
15.0-15.9	3	5	40-42.9	3	3
16.0-16.9	2	2	43-45.9	5	4
17.0-17.9	1	1	46-48.9	2	2
			49-51.9	2	2
			52-54.9	0	1
			55-57.9	0	2
			58-60.9	2	0
			61-63.9	1	1
			64-66.9	0	0
			67-69.9	0	1
			70-72.9	0	0
			73-75.9	1	0
	Mean, 14.0	Mean, 13.9		Mean, 43.2	Mean, 43.5
	Median, 13.8	Median, 13.8		Median, 40.5	Median, 41.3
	Mode, 13+	Mode, 13+		No mode	Mode, 37+
	M.D., 1.07 sec.	M.D., 1.22 sec.		M.D., 1.84 sec.	M.D., 7.45 sec.
	S.D., 1.35 sec.	S.D., 1.52 sec.		S.D., 10.2 sec.	S.D., 9.8 sec.
	P.E., 0.9 sec.	P.E., 1.0 sec.		P.E., 6.8 sec.	P.E., 6.6 sec.

M.D. = mean deviation (from median); S.D. = standard deviation; P.E. = probable error.

* Note the fair parallelism of concentration and distribution of plasma and marrow figures in both phases.

endothelial system is not involved in the production of prothrombin. There are several arguments which might be used against such a conclusion. One might claim that this comparative method is not trustworthy, although it has been used satisfactorily before. The venous blood departing from an organ may be found to have a higher concentration of some constituent than arterial blood entering the same organ if that constituent is manufactured or stored in the organ, e. g., angiotonin and the kidney. Measurement of prothrombin concentrations of pulmonary arterial and pulmonary venous blood in animals has shown a lower concentration in the venous blood, leading certain workers to believe that the lung is one organ which serves to destroy

prothrombin.[2] An argument for specificity of action of the reticulo-endothelial cells in varying locales is untenable in the light of present knowledge. One might wonder whether the process of elaboration of prothrombin is slow and/or irregular, thus making it impossible by the means at hand to measure differences in concentration from that of the peripheral blood. Then, again, it is possible that a higher concentration of prothrombin in the marrow may be obscured by dilution of the aspirated marrow with whole blood from the venous channels and with lipid material.

In order to circumvent the last two possibilities, it was decided to study another group of patients receiving high doses of synthetic vitamin K. This dosage serves the purpose of considerably increasing the prothrombin level of the blood at least for a few days and therefore presumably augments the production of prothrombin. Table 3 is a compilation of the results determined in this group of 8 patients.

TABLE 3.—*Changes in the Plasma and Marrow Times After Vitamin-K-Like Quinones* *

Sub-ject No.	Prothrombin Time, Whole, Seconds		Plasma> Marrow— Plasma< Marrow+	> than Significant < than Significant	Prothrombin Time, Diluted 12.5%, Seconds		Plasma> Marrow— Plasma< Marrow+	> than Significant < than Significant
	Plasma	Mar-row			Plasma	Mar-row		
K1	12,0	12,5	+0.5	=	36.5	38.0	+1.5	=
K2	12.4	10.9	—1.5	>	37.6	36.2	—1.4	=
K3	11.5	11.9	+0.4	=	35.0	39.9	+4.9	=
K4	11.8	11.1	—0.7	=	33.4	35.0	+1.6	=
K5	13.7	13.1	—0.6	=	33.4	33.5	+0.1	=
K6	10.6	11.2	+0.6	=	40.0	35.4	—4.6	=
K7	9.6	10.4	+0.8	=	36.8	42.5	—5.7	<
K8	11.0	10.7	—0.3	=	37.9	41.0	+3.1	=
Average	11.6	11.5	Diff. 0.68		36.3	37.8	Diff. 2.9	

* The quinone definitely lessened the averages of the plasma and marrow prothrombin times as contrasted with the control studies (table 1).

All these subjects had had large doses of vitamin-K-like quinone (25 to 100 mg. a day orally for a week or 72 to 200 mg. intravenously twenty-four hours prior to the sternal marrow puncture). This table shows that the quinone was efficacious, for the averages of the prothrombin times of plasma and marrow in both phases are decidedly less than in the control group (table 1). The average differences and percentage average differences remain about the same as in the control group (table 4), as do the general characteristics of the group.

2. Andrus, W. DeW.; Lord, J. W., Jr., and Kaeur, J. T.: Studies on the Fate of Plasma Prothrombin, Science **91**:48, 1940.

This is evidence that even during a period of rapidly increasing production of prothrombin no difference of any import is found between marrow and peripheral blood. This observation adds strong support to the contention that the bone marrow and reticuloendothelial system are not involved in the metabolism of prothrombin.

TABLE 4.—*Comparison of Average Prothrombin Time*

	No Medication	Vitamin K	Dicoumarin
Average plasma, whole..................	14.0 seconds	11.6 seconds	18.8 seconds
Average marrow, whole.................	13.9 seconds	11.5 seconds	20.8 seconds
Average plasma, diluted................	43.2 seconds	36.3 seconds	84.7 seconds
Average marrow, diluted................	43.5 seconds	37.8 seconds	99.4 seconds
Average difference, whole..............	0.76 seconds	0.68 seconds	2.0 seconds
Average difference, diluted.............	2.95 seconds	2.9 seconds	14.6 seconds
Per cent average difference, whole........	5.4 per cent	5.9 per cent	10 per cent
Per cent average difference, diluted......	6.9 per cent	7.8 per cent	15.9 per cent

A third series of measurements was made on 7 patients who had effective doses of dicoumarin (400 to 600 mg.) given in the forty-eight hour period preceding sternal puncture. As seen in table 5 the tendency in this group was not only the expected prolongation of prothrombin time but a dissociation of effect on plasma and marrow, with 71 per cent (5 of 7) having a significant difference in the undiluted fraction and 86 per cent (6 of 7) in the diluted fraction. In table 4

TABLE 5.—*Changes in the Prothrombin Time After Ingestion of 400 to 600 Mg. of Dicoumarin* *

Subject Number	Prothrombin Time, Whole, Seconds		Plasma > Marrow — Plasma < Marrow +	> than Significant < than Significant	Prothrombin Time, Diluted (12.5%), Seconds		Plasma > Marrow — Plasma < Marrow +	> than Significant < than Significant
	Plasma	Marrow			Plasma	Marrow		
D1	17.2	19.3	+2.1	<	59.1	69.9	+10.8	<
D2	14.2	16.0	+1.8	<	44.6	51.3	+ 6.7	<
D3	40.4	No clot	?	<	231.0	274.0	+43.0	<
D4	36.6	41.4	+4.8	<	95.5	118,4	+22.9	<
D5	16.2	16.9	+0.7	=	53.4	60.8	+ 7.4	<
D6	13.8	16.3	+2.5	<	48.7	51.3	+ 2.6	=
D7	14.8	14.7	—0.1	=	60.5	69.5	+ 9.0	<
Average	18.8	20.8			84.7	99.4		
Average difference.........			2.0				14.6	

* Note the dissociation of effect on plasma and marrow prothrombin times.

the important facts concerning each of the 3 groups thus far discussed are presented, and the only percentage average difference to exceed the previously established significant level is in the dicoumarin column.

It is difficult to conceive that this difference is due to inhibition of prothrombin formation in the marrow, for that would be almost totally inconsistent with the results of the first two group studies. It would be much more consonant with our general observation to postulate

that the dicoumarin serves to hasten the process of destruction of prothrombin, and it would appear that this is most probably done by the reticuloendothelial system.

The fourth and last group of subjects were studied in a like manner to determine the effect of simultaneous doses of synthetic vitamin K and dicoumarin. Table 6 presents results for this group. All the

TABLE 6.—*Effect of Simultaneous Doses of Quinone and Dicoumarin on the Prothrombin Studies*

Subject Number	Prothrombin Time, Whole, Seconds		Plasma > Marrow — Plasma < Marrow +	> than Significant < than Significant	Prothrombin Time, Diluted (12.5%) Seconds		Plasma >_ Marrow — Plasma < Marrow +	> than Significant < than Significant
	Plasma	Marrow			Plasma	Marrow		
KD1	13.3	12.2	—1.1	=	44.0	49.0	+ 5.0	=
KD2	12.5	13.9	+1.4	<	53.0	61.3	+ 8.3	<
DK3	19.0	20.8	+1.8	<	69.3	80.3	+11.0	<
DK4	27.9	29.7	+1.8	=	164.5	191.6	+27.1	<
DK5	26.2	29.4	+3.2	<	86.2	101.7	15.5	<

subjects received massive doses of the quinone (150 to 250 mg.) intravenously and amounts of dicoumarin varying from 100 to 600 mg. in the order of their listing on the chart. This series yielded results similar to those of the group receiving dicoumarin alone (refer to table 7), 60 per cent (3 of 5) significant prolongations of the prothromthrombin time for marrow in the undiluted plasma fraction and 80 per cent (4 of 5) in the diluted plasma. The only patient with no pro-

TABLE 7.—*Comparative Changes in the Plasma and Marrow Prothrombin Times*

	Whole			Diluted		
	Plasma > Marrow	P = M	P < M	Plasma > Marrow	P = M	P < M
Patients with no medication.	2 (7%)	24 (86%)	2 (7%)	1 (4%)	25 (89%)	2 (7%)
Patients with vitamin K......	1 (14%)	7 (86%)	0 (0%)	0 (0%)	7 (86%)	1 (14%)
Patients with dicoumarin....	0 (0%)	2 (29%)	5 (71%)	0 (0%)	1 (14%)	6 (86%)
Patients with vitamin K and dicoumarin.................	0 (0%)	2 (40%)	3 (60%)	0 (0%)	1 (20%)	4 (80%)

longation in either phase was KD 1, who had received only 100 mg. of dicoumarin, the smallest amount administered to any of the group. Though the end effects of synthetic vitamin K and dicoumarin are oppposite, one increasing prothrombin concentration, and the other decreasing it, the manner of action of the latter does not seem to be directly antagonistic to the former. Even when the dose of dicoumarin is small and that of the quinone massive, the reaction of the dicoumarin usually predominates in that the prothrombin time of marrow plasma decreases disproportionately to that of the peripheral blood, although

the large amount of synthetic vitamin K may have prevented the absolute prothrombin time from rising prominently. The impression is gained that the dicoumarin produces the effect not solely by prohibiting the formation of prothrombin but also by facilitating its destruction. If the former were true we would expect to find not a differential prothrombin concentration in marrow and plasma but rather a symmetric decrease in both, for in circumstances of normal synthesis of prothrombin it is symmetric in both. On the other hand, if the action of dicoumarin were also to help destroy prothrombin in the reticuloendothelial system, the concentration at the marrow would decrease faster in the marrow than in the blood regardless of whether or not synthetic vitamin K were given.

CONCLUSIONS

1. From the evidence presented we are led to conclude that prothrombin is not elaborated by the reticuloendothelial system and therefore is probably not a function of the hepatic parenchyma.

2. Prothrombin is equally distributed in the sternal marrow and in the more actively circulating peripheral blood stream and may be much more widely disseminated throughout the body than is generally realized.

3. Vitamin K accelerates the production of prothrombin and the excess which results is also equally distributed in the marrow and peripheral blood.

4. Dicoumarin causes a more pronounced decrease in prothrombin of the marrow than in prothrombin of the peripheral blood. The evidence compiled herein is suggestive that this is due to the destruction of prothrombin, most likely by the reticuloendothelial system.

5. When dicoumarin is given simultaneously with synthetic vitamin K, even if the former is in relatively small amounts and the latter in massive quantities, the action of the dicoumarin usually predominates.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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(Concluded from page 364)

PENICILLIN

Experimental.—An organized cooperative study of the effect of penicillin in experimental syphilis of rabbits is under way in several laboratories in this country (Eagle, Mahoney, Chesney, Carpenter, Rake, Fleming). Here are being explored the essential time-dose relationships, the combination of penicillin with other chemotherapeutic agents, the effect of different penicillin fractions and of possible impurities and commercial penicillin and optimum treatment schedules. Except as cited later, however, none of the mentioned investigators has as yet published results, which may be expected to be forthcoming during this next year. Meanwhile, only two very unsatisfactory papers dealing with the general problem of penicillin in early syphilis of rabbits have appeared, those of Selbie and Simon,[62] working in Great Britain, and Ercoli and Lafferty,[63] in this country.

Selbie and Simon [62] have employed penicillin in the treatment of 9 rabbits with testicular chancres. One animal received a single intramuscular injection of 400 units per kilogram of weight. Five animals received three injections at three hourly intervals with a total dose ranging from 1,500 to 30,000 units per kilogram (total duration of treatment six hours). Another animal received five daily injections to a total of 2,500 units per kilogram. The remaining 2 were given three injections at three hourly intervals on each of four successive days to a total of 12,000 units per kilogram. Spirochetes disappeared from the lesions within one to seven days in 8 of the 9 animals, and lesions healed completely in 3, though there was only temporary regression

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62. Selbie, F. R., and Simon, R. D.: The Effect of Penicillin on Treponema Pallidum Infection in Rabbits, Brit. J. Exper. Path. **25**:229 (Dec.) 1944.

63. Ercoli, N., and Lafferty, L. C.: The Anti-Spirochetal Activity of Penicillin in Experimental Infections, Proc. Soc. Exper. Biol. & Med. **57**:4 (Oct.) 1944.

or no effect in the other 6. In 5 of the treated animals whose lesions showed only temporary regression, spirochetes could again be found by dark field examination in thirty-five to forty-nine days after treatment. No information is provided as to eventual cure, since transfers of lymph nodes were not performed. It is certain, however, that 6 of the 9 animals were not cured, since lesions either failed to heal at all or subsequently relapsed. The authors studied blood levels in 5 rabbits after the intramuscular injection of graded doses and believe that it requires approximately five times as much penicillin in the rabbit as in man to produce comparable bacteriostatic titers. They are inclined to attribute the unfavorable results obtained in their animals to this factor. Actually, however, their poor results seem to us to be based on too short a duration of treatment and on too irregular spacing of multiple injections, so that maintained blood levels were not produced.

Ercoli and Lafferty [63] found in 9 animals that the intravenous injection of the sodium salt of penicillin in single doses of 33,000 to 47,000 units per kilogram resulted in the disappearance of T. pallidum, as determined by dark field examination, in experimental rabbit syphilis within an eighteen hour period. A similar effect could be obtained with an approximate total dose of 16,000 units per kilogram administered intravenously in four divided doses at unstated but probably irregular intervals, over a seventy-two hour period. However, even total doses of 132,000 to 282,000 units per kilogram of weight given in four to six injections over forty-eight to seventy-two hours were not curative, since in 4 of 9 animals transfers of lymph nodes produced syphilis at an unstated interval after treatment. Nothing is said of the other 5 animals.

In view of the demonstrated efficacy of penicillin in the treatment of syphilis and other spirochetal diseases, it is important to determine whether this therapeutic effect requires the intervention of body cells, or whether it is due to a direct spirocheticidal action. With other micro-organisms, inhibitory, bacteriostatic and an actual bactericidal action have been described.

Eagle and Musselman [64] have tested the spirocheticidal activity of penicillin against four cultured strains of T. pallidum. They summarize by saying:

1. Penicillin was found to be actively spirocheticidal *in vitro* against the Reiter, Kazan, Nichols, and Noguchi strains of so-called *S. pallida,* and a strain of mouth spirochetes. The threshold concentration was 0.01 unit per cc. (1-160,000,000 penicillin). The rate and degree of action increased with the concentration of penicillin up to a level of approximately 0.1 to 0.25 unit per cc., which rendered more than

64. Eagle, H., and Musselman, A. D.: The Spirocheticidal Action of Penicillin in Vitro and Its Temperature Coefficient, J. Exper. Med. **80**:493 (Dec.) 1944.

99 per cent of the organisms nonviable within 12 hours. Higher concentrations did not appreciably accelerate the effect.

2. Within the range $4 \times 10^4 - 10^7$ organisms per cc., the initial rate at which the spirochetes were killed was not affected by their number. Consistent with that observation, no demonstrable penicillin was found or inactivated by thick suspensions. The amount of penicillin required to sterilize suspensions of varying density nevertheless varied to a large extent with the initial number of organisms. This was only in part due to the progressive deterioration of the penicillin with prolonged incubation; and the persistence of organisms resistant to the drug, and perhaps an adaptative change after prolonged exposure to penicillin, may be contributing factors.

3. The organisms remained actively motile for a period of 8 to 24 hours after they had been rendered non-viable by the action of penicillin. Even 500 units of penicillin per cc., or approximately 10,000 times an effectively spirocheticidal concentration, did not accelerate that delayed immobilization. It follows that, although penicillin rapidly renders the organisms non-viable, the metabolic system affected is not immediately essential to the life of the cell, and the motility and presumably other vital functions remain unaffected for a significant number of hours.

4. The rate at which the organisms were killed by penicillin increased with temperature in the range $8 - 40°$ C. With an original inoculum of 10^6 spirochetes per cc., the percentage of organisms surviving after 24 hours at $39 - 40°$, $36 - 37°$, $32 - 33°$, $22 - 23°$, and $8°$ C. was 0.02, 0.2, 1, 10, and 100 respectively; and those results were independent of the concentration of penicillin in the range 0.25 to 250 units per cc. If these observations with a non-pathogenic organism *in vitro* are applicable to the pathogenic organism *in vivo*, they suggest that the combined use of fever and penicillin in the treatment of syphilis may be more effective than either alone.

There is no published information concerning the exact composition of the various brands of crude penicillin. It is already known, however, that there is more than one type of crystalline penicillin. At least three of those fractions, F, G and X, have been mentioned in the current literature [65] without details of the chemistry of production. It has been stated that the proportions of these fractions present in commercial penicillin vary depending on the method of production. In view of these facts the question arises as to which penicillin fraction is responsible for the therapeutic effects, or indeed whether some substance other than penicillin itself might not be responsible. Dunham and Rake [66] performed experiments in vitro and in vivo to determine whether penicillin G or impurities present in partially purified penicillin may contribute to the antisyphilitic action of the mixtures. The immobilizing activities in vitro of ampules of commercial penicillin, old preparations of low potency and an aluminum oxide adsorbate of low potency obtained

65. Dale, H.: Address of the President of the Royal Society, Science **101**:23 (Jan. 12) 1945.

66. Dunham, W. B., and Rake, G.: The Relative Activity of Partially Purified Penicillin and of Crystalline Penicillin G on Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **29**:214 (March) 1945.

in the chromatographic purification of commercial penicillin and crystalline penicillin G were compared. Crystalline penicillin G employed in a concentration of 8,800 units per cubic centimeter for two hours in vitro had little or no effect on the motility of T. pallidum. Under the same conditions, a solution containing 2,200 units per cubic centimeter of the least pure penicillin preparation immobilized all of the spirochetes. A substance in partially purified penicillin that immobilized spirochetes could be concentrated by adsorption on aluminum oxide and recovered by elution. The concentration of the substance in partially purified penicillin that was active against spirochetes in vitro was only very slightly, if at all, reduced by incubation at 37 C. (98.6 F.) in the presence of a weak solution of penicillinase over a period of eleven days. Under these conditions a large proportion of the penicillin present is inactivated. The immobilization of spirochetes in vitro by partially purified penicillin was due, therefore, to one or more of the impurities present. Penicillin acid, a product of the hydrolysis of pure penicillin G, was inactive.

Virulent spirochetes exposed to 1,100 units per cubic centimeter of partially purified penicillin were noninfectious for rabbits despite persistent motility (compare the observation of Eagle and Musselman that penicillin renders culture spirochetes nonviable while motility is still present) while spirochetes similarly exposed to 800 units per cubic centimeter of crystalline penicillin G produced orchitis in rabbits.

Partially purified penicillin, 330 units per milligram, protected a large proportion of rabbits from local and generalized infection when 66,000 units per kilogram of body weight were administered intramuscularly five hours after a suspension of spirochetes had been rubbed into an incision in the skin of the back. The same dose of crystalline penicillin G failed to protect. That crystalline penicillin G does have some antisyphilitic action was shown by the prevention of local syphilitic lesions in a large proportion of rabbits treated with injections of 166,000 units per kilogram of weight. In the same experiment, however, an aluminum oxide adsorbate of partially purified penicillin showed greater activity.

The general trend of the experiments in vitro and in vivo which have been discussed indicates that crude penicillin is more effective in the treatment of syphilis in rabbits than is highly purified penicillin when an equal number of units is employed. This suggests that certain impurities or fractions of penicillin, other than penicillin G, contribute to the antisyphilitic action of commercial penicillin.

These experiments also suggest that, because of the large quantities that would be required, it would not be practicable at the present time to employ penicillin in a single dose systemically as a prophylactic against syphilis in human beings.

This is disturbing information to those interested in the use of penicillin for syphilis. In acute infections (e. g., gonorrhea, pneumonia, meningitis) commercial penicillin as now available seems eminently satisfactory, and it is perhaps of academic interest only as to which component of the mixture of many is actively bactericidal. In the more chronic infections, e. g., subacute bacterial endocarditis and syphilis, it may prove to be of paramount importance to determine whether it is penicillin itself, and if so which fraction thereof, or some impurity contained in commercial penicillin which is actually most effective. Work is in progress on these points, but data are not as yet available.

Heilman[67] studied the therapeutic effect of streptomycin on experimental relapsing fever in mice and leptospirosis icterohaemorrhagica in hamsters. The investigator used large doses of streptomycin in both *sets of experiment. He concluded that streptomycin exerted a considerable protective effect against experimental infections with both Borrelia novyi and Leptospira icterohaemorrhagiae. However, the drug was relatively less effective than penicillin in the treatment of these infections. This is the first report which would indicate that streptomycin has antispirochetal properties.

Methods of Administration. — Absorption-Delaying Methods: Although clinical effectiveness of penicillin has been well established, a completely satisfactory method of administration of the drug has not been found.

The intramuscular injection of aqueous or saline solutions, most commonly employed, results in high blood levels of penicillin for brief periods and necessitates frequent injections. The intermittent intravenous method also results in transitory high levels and necessitates repeated venipunctures. The continuous intravenous or intramuscular drip, although maintaining a satisfactory level, is technically difficult, immobilizes the patient and is frequently productive of local reactions.

Romansky and Rittman[68] feel that a method of administration of penicillin which would decrease the rate of absorption and prolong the duration of an effective level in the blood, in addition to being of minimum inconvenience to the patient, would be of importance, especially in the treatment of syphilis. To this end they experimented with suspensions of penicillin in refined peanut, sesame, cottonseed, corn, castor and olive oils, and protamine zinc in an attempt to produce its prolonged action in rabbits after intramuscular injection. All of these resulted

67. Heilman, F. R.: Streptomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil's Disease), Proc. Staff Meet., Mayo Clin. **20**:169 (May 30) 1945.

68. Romansky, M. J., and Rittman, G. E.: Penicillin: I. Prolonged Action in Beeswax-Peanut Oil Mixture; II. Single Injection of Treatment of Gonorrhea, Bull. U. S. Army M. Dept., October 1944, no. 81, p. 43.

in more prolonged blood levels than were obtained with salt solutions of the drug.

Having in mind the pioneer work of Code and his associates [69] on the absorption-delaying effect of beeswax dissolved in various oils in the administration of histamine and other substances, Romansky turned to this expedient:

After preliminary trials with varying amounts of yellow wax U. S. P. (beeswax) in different oils, the most satisfactory results were obtained with a beeswax–peanut oil mixture. Because calcium penicillin is less hygroscopic than the sodium salt and forms better mixtures with the oils, it was used for the majority of experiments. The method of suspending penicillin in beeswax–peanut oil mixture is given.

As a pilot experiment rabbits weighing from 2.5 to 3.5 Kg. were given injections intramuscularly of 5,000 to 10,000 Oxford units of penicillin contained in 1 cc. of beeswax–peanut oil mixture, and blood assays were made to determine the duration and maintenance of effective levels. This experiment showed that after the administration of 5,000 units of sodium penicillin in saline solution the blood level rapidly reaches 1.25 units per cubic centimeter and rapidly drops to zero within two hours. When the same amount of penicillin is suspended in peanut oil alone, a level of 0.312 unit per cubic centimeter of blood is reached within approximately one-half hour and is maintained for a longer period than with the saline solution, approximately three hours. If, on the other hand, the penicillin is suspended in beeswax–peanut oil mixture, penicillin can be demonstrated for as long as six hours.

Human subjects were then given single injections of 41,500 to 66,400 Oxford units of penicillin intramuscularly in the buttocks. These doses were contained in 2 to 2.4 cc. of beeswax–peanut oil mixtures. Again, satisfactory blood levels were maintained for six to seven hours.

Since the experimental results with the penicillin beeswax–peanut oil mixture were so favorable, it was deemed advisable to treat 12 patients with gonococcic urethritis. Three of these had had no previous treatment, and 9 were resistant to sulfonamide drugs. All were treated with a single injection of the penicillin beeswax–peanut oil mixture. Doses varied between 51,250 and 100,000 Oxford units contained in 2 to 3 cc. of the mixture. As the total dosage of penicillin was increased, the period over which penicillin could be demonstrated in the blood was also prolonged. When 100,000 units was given in a single injection, penicillin could be demonstrated in the blood for as long as ten hours and was excreted in the urine for as long as twenty-five hours. There was only 1 failure in the 12 patients treated. This was in a previously

69. Code, C. F.; Gregory, R. E. L., and Kottke, F. J.: Prolonged Action of Desoxycorticosterone Acetate, Am. J. Physiol. **133**:240 (Jan.) 1941.

untreated patient who received the smallest dose of penicillin, 51,250 Oxford units. The size of the dose does not entirely explain the failure, since the levels obtained in the blood compare favorably with the levels of patients who received somewhat larger doses of penicillin and were cured.

None of the patients complained of local pain or irritation in the region of injection.

Intramuscular injections of 500 to 1,000 Oxford units of penicillin, contained in 0.05 to 0.10 cc. of 3 per cent beeswax–peanut oil mixture, were given to 10 hamsters twice a day for five days. The animals were then killed at the rate of 1 a week for the purpose of examining the tissue from the site of injection. There was no necrosis of muscle demonstrated, and only minimal changes were noted. Generally small oil cysts from 1 to 2 mm. in diameter could be identified after the seventh day. By the thirtieth day the walls of the cysts were less cellular, and some were partially collapsed.

A later paper by Romansky, Murphy and Rittman [70] expands the results of the single injection treatment of gonorrhea with calcium penicillin in peanut oil–beeswax and is mentioned here because of the possible applicability of the method to syphilis.[71] Among 100 patients receiving a single dose of 100,000 units, 93 were cured; the 7 who were not cured responded to a second single injection of 150,000 units. All of 75 patients receiving a single dose of 150,000 units were cured.

Blood levels and duration and amount of excretion of penicillin in the urine after larger single injections of penicillin are graphically recorded in the figure. Romansky [72] has permitted us to reproduce this figure, which will appear in an article to be published in the *New England Journal of Medicine*.

Fears that beeswax might contain pollens and therefore create a hazard in the treatment of pollen-sensitive sufferers from hay fever or asthma have been allayed by careful experimentation by Gay.[73]

70. Romansky, M. J.; Murphy, R. J., and Rittman, G. E.: Single Injection Treatment of Gonorrhea with Penicillin in Beeswax-Peanut Oil: Results in One Hundred and Seventy-Five Cases, J. A. M. A. **128**:404 (June 9) 1945.

71. Calcium penicillin so prepared in peanut oil—beeswax (4.8 per cent beeswax by weight) is now commercially available. One firm calls this product "Delicillin" ("del", delayed). Physicians should be cautioned that while it has been experimentally employed in the treatment of a small number of patients with early syphilis, the results are not yet available, and the method cannot as yet be recommended for general use.

72. Romansky, M. J.: New England J. Med., to be published.

73. Gay, L. N.: The Nonantigenic Property of Beeswax, J. Allergy **16**:192 (July) 1945.

Various other methods of delaying absorption or retarding excretion of penicillin (bibliography given by Bronfenbrenner and Favour[74]) have been tried, but none seems as promising, in syphilis at least, as Romansky's method.

Oral or Rectal Administration: A number of papers have already appeared dealing with the oral or rectal administration of penicillin (Libby[75]; Burke, Ross, and Strauss[76]; György and his associates[77]; Loewe and his group[78]; McDermott and associates,[79] and Charney and others[80]—see comments following). All of these indicate that when
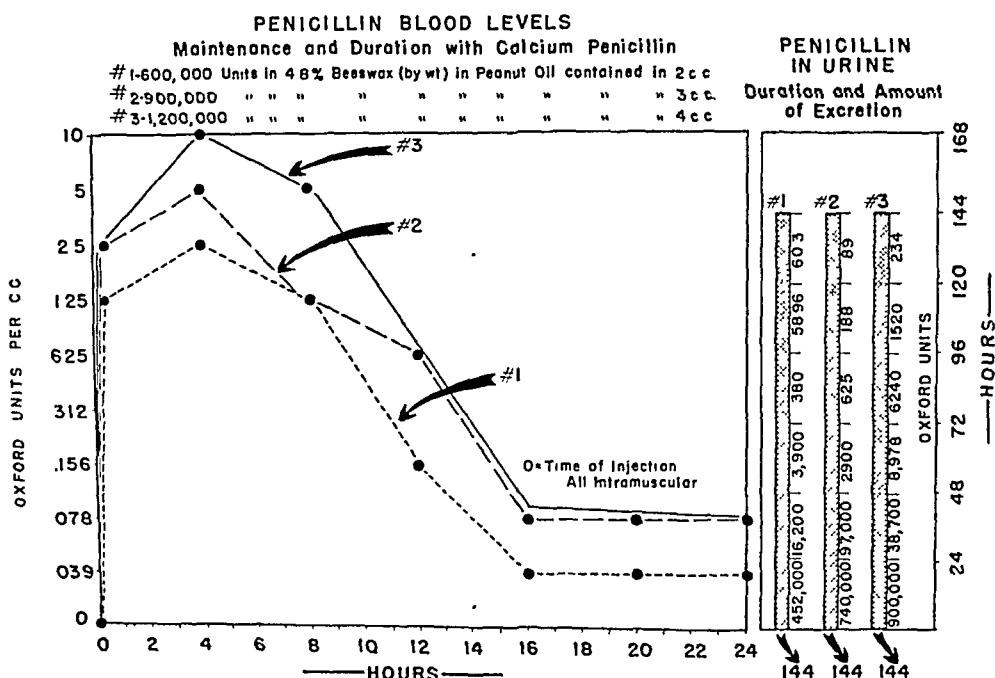
Penicillin in blood and duration and amount of excretion in urine after large single injections of the drug.

74. Bronfenbrenner, J., and Favour, C. B.: Increasing and Prolonging Blood Penicillin Concentrations Following Intramuscular Administration, Science 100: 673 (June 29) 1945.

75. Libby, R. L.: Oral Administration of Penicillin in Oil, Science 101:178 (Feb. 16) 1945.

76. Burke, F. G.; Ross, S., and Strauss, C.: Oral Administration of Penicillin: A Preliminary Report, J. A. M. A. 128:83 (May 12) 1945.

77. György, P.; Vandegrift, H._N.; Elias, W.; Colio, L. G.; Barry, F. M., and Pilcher, J. D.: Administration of Penicillin by Mouth: Preliminary Report, J. A. M. A. 127:639 (March 17) 1945.

78. Loewe, L.; Alture-Werber, E., and Rosenblatt, P.: Administration of Penicillin by Rectal Suppository: Preliminary Note, J. A. M. A. 128:18 (May 5) 1945.

79. McDermott, W.; Bunn, P. A.; Benoit, M.; DuBois, R., and Haynes, W.: Oral Penicillin, Science 101:228 (March 2) 1945.

80. Charney, J.; Alburn, H. E., and Bernhart, F. W.: Urinary Excretion of Penicillin in Man After Oral Administration with Gastric Antacids, Science 101:251 (March 9) 1945.

penicillin is administered orally at appropriately spaced intervals, either as such in solution or in capsules or in combination with various antacids or suspended in oils with or without beeswax, blood levels may be obtained comparable to those achieved after a parenterally administered dose about one fifth as large. Absorption from the rectum is, however, poor. The details of these papers are purposely omitted here, since my colleagues and I believe that, except in most exceptional circumstances, the oral treatment of syphilis with penicillin or any other drug is at present indefensible. Syphilitic patients, regardless of intelligence, cannot be trusted to take oral medication at the appropriate intervals (with penicillin, every two to three hours day and night) for the necessary length of time. The prescription is sometimes not filled at all; if the drug is obtained, the urgent necessity for regularity in taking it is often—perhaps nearly always—quickly forgotten, and the bottle reposes peacefully on the bathroom shelf. This is to say nothing of the fact that if used orally in syphilis, prohibitively larger and expensive amounts of penicillin would certainly be required—perhaps a minimum of 10,000,000 units and a possible maximum of several hundred million units.

The Intrathecal Administration of Penicillin: That penicillin cannot be demonstrated in the cerebrospinal fluid after parenteral administration has frequently been demonstrated. This has led to the routine intrathecal administration of the drug in most cases of bacterial meningitis and in situations in which there appears to be some advantage to the method. In neurosyphilis the desirability of intrathecal treatment with other substances than penicillin has long been a controversial subject, on which there is still no complete unanimity of opinion. Nevertheless it was inevitable that penicillin should be so emphasized in neurosyphilis; unfortunately so, since careful studies have not been carried out as to safe doses, either for animals or for men.

Pilcher and Meacham [81] have studied the effects of intracisternal injection of penicillin in normal dogs, using doses of 50 to 500 units. Such injections produced transitory "meningeal reactions," whose intensity was roughly proportional to the dose. These reactions apparently consisted in an increase in the spinal fluid cell count ranging roughly from 1,000 to 16,000 cells per cubic millimeter, occurring at its maximum two to six hours after injection. No significant neurologic or other clincal phenomena were obseved. In a footnote Pilcher and Meacham say that later observations to be published elsewhere have shown that much larger and more frequent intrathecal doses are well tolerated. So far as we

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81. Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infections: III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin, J. A. M. A. **123**:330 (Oct. 9) 1943.

are aware, these later observations have not yet appeared in print. It is known that other experimental studies, also so far unpublished, have shown that penicillin locally applied to the central nervous system (brain or spinal cord) has certain irritating properties which may produce acute or chronic reactions with convulsions, coma and death.

A safe dosage of penicillin intrathecally for man has not yet been determined. Most workers suggest a maximum of 20,000 units. That there may be grave risk in the administration of this or of larger amounts is exemplified by certain papers dealing with the treatment of neurosyphilis, discussed in later paragraphs. There is also a strong suggestion in studies of neurosyphilis so far reported (see later comments on Nelson and Duncan) that the intrathecal use of penicillin in neurosyphilis is unnecessary.

For the time being and until further and more detailed clinical and experimental studies have been completed, we feel strongly that the average physician would be wise to avoid the method entirely in neurosyphilis.

The Penetration of Penicillin into Various Tissues, Especially the Eye.—Several groups of workers have studied the penetration of penicillin into various structures of the eye after the parenteral and local administration of penicillin. Struble and Bellows [82] found that penicillin could be detected in the eyeball of dogs within fifteen minutes after 12,800 units per kilogram was injected intravenously. The ocular tissues and fluids are listed in accordance with the concentrations in them of penicillin, in decreasing order: extraocular muscles, sclera, conjunctiva, tears, chorioretinal layer, aqueous humor, vitreous humor and cornea. The crystalline lens contained none. Levels in the aqueous humor and the less vascularized tissues, such as the conjunctiva and sclera, after their initial sharp rise within the first fifteen minutes, continued to increase slowly until the end of the first hour. Barely a trace of penicillin remained in the eyeball after three hours.

When penicillin was administered intravenously and intramuscularly in amounts comparable to therapeutic doses (1,500 units per kilogram), there was such a slight concentration in the fluids and tissues of the eye that it was not measurable by the usual methods.

After subconjunctival injection (500 to 5,000 units in 0.25 cc. of saline solution) high and even enormous concentrations were reached in the cornea, iris, ciliary body, conjunctiva and sclera. There was a moderate amount in the aqueous and vitreous humors. No drug was demonstrated in the posterior half of the chorioretinal layer and the

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82. Struble, G. C., and Bellows, J. G.: Studies on the Distribution of Penicillin in the Eye, and Its Clinical Application, J. A. M. A. **125**:685 (July 8) 1944.

lens. After a constant corneal bath of penicillin (20,000 units per cc.), the results were similar, except that the concentrations in the aqueous, cornea, vitreous and iris with the ciliary body were higher, and those in the conjunctiva and sclera were lower.

Von Sallmann and Meyer [83] compared the penetration of penicillin into the aqueous humor of rabbits after local application by means of iontophoresis with that following a corneal bath with and without wetting agents. The ionization method increased the concentration of penicillin in the aqueous ten times as much as the corneal bath and about eight times as much as the corneal bath with the addition of a wetting agent, Aerosol 1B (dibutyl sodium sulfosuccinate). After a single iontophoretic application of a 0.25 per cent solution of the sodium salt of penicillin, the aqueous exhibited an antibacterial activity for almost four hours; after a single corneal bath with a solution of the same concentration, the antibacterial activity continued little more than two hours.

Leopold and LaMotte [84] found that, although penicillin locally applied to the eye in solution or in ointment fails to penetrate into the aqueous humor of the normal rabbit eye after one instillation, it does penetrate readily into the anterior chamber of rabbit eyes with corneal abrasions or ulcers. The concentrations obtained in the anterior chamber of the eyes with inflamed or abraded corneas after local instillation of 500 units of penicillin per cubic centimeter in isotonic solution of sodium chloride or 500 units per gram of ointment base exceed the probable antibacterial level of 0.15 unit per cubic centimeter. They believe that it is not necessary to resort to iontophoresis, the corneal bath technic or subconjunctival injection in order to obtain effective concentrations of penicillin in the aqueous humor of eyes with infected corneal ulcers or abrasions. Instillation of a solution of penicillin (500 units per cubic centimeter of isotonic solution of sodium chloride) or penicillin ointment (500 units per gram) need be made only once every two hours to the conjunctival cul-de-sac to maintain high concentrations in the aqueous humor. It was also demonstrated that repeated applications of penicillin solution do not significantly retard regeneration of corneal epithelium.

These three studies are of potential (but not as yet demonstrated) importance in the local penicillin treatment of interstitial keratitis, a manifestation of syphilis which does not respond readily to the parenteral administration of the drug.

83. von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, Arch. Ophth. **31**:1 (Jan.) 1944.

84. Leopold, I. H., and LaMotte, W. O., Jr.: Penetration of Penicillin in Rabbit Eyes with Normal, Inflamed and Abraded Corneas, Arch. Ophth. **33**:43 (Jan.) 1945.

More important to the syphilotherapeutist, however, are the only experiments so far recorded concerning the concentrations of penicillin in various tissues of the body. Struble and Bellows [82] treated an unstated number of dogs with a single large (12,800 units per kilogram) intravenous injection (corresponding to 'a single dose of nearly 1,000,000 units to an adult) and killed the animals one, two and three hours afterward. The body tissues and fluids examined are listed in accordance with the concentration in them of penicillin, in decreasing order: kidney, small intestine, lung, buccal mucosa, bile, skin, liver, adrenal gland, heart, voluntary muscle and spleen. None, or only traces, could be found in nerve tissue, cerebral dura and bone marrow. At the end of three hours all the tissues and fluids examined, except bile, showed little or no penicillin.

Penicillin in the Treatment of Syphilis:—Since penicillin has been used in the treatment of syphilis on a considerable scale for only twenty-three months at the date of this writing (Sept. 1, 1945), it is still too early to expect the appearance of any but the most preliminary sort of results. The next two to five years should see them expanded into more definite pronouncements.

After a brief historical review of the chemotherapy of syphilis, Moore [85] describes the nationwide cooperative study of penicillin in syphilis which is in progress under the auspices of the Committee on Medical Research of the Office of Scientific Research and Development and of the National Research Council. Together with the Army, the Navy and the Public Health Service, some twenty-five civilian clinics were invited to participate in a study of the effect of penicillin on early and late syphilis, the results in early syphilis to be pooled and statistically analyzed as a group. In addition, the cooperation of four laboratories was enlisted in order to study in experimentally infected animals the various permutations of the time-dose relationship in both early and late syphilis; to study such other important issues as the effect of penicillin in combination with other chemotherapeutic agents, such as arsenic and bismuth, or in combination with fever, as well as to engage in other important pharmacologic investigations.

The results to the date of the presentation of the preliminary report on this study (October 1944) permit a number of general statements. Several thousand patients with early syphilis had then been treated, but only a few hundred of them had been followed six months or longer. Treatment was by the intramuscular route with injections every three to six hours. The only factor which has so far proved of importance

85. Moore, J. E.: The Chemotherapy of Syphilis, Bull. New York Acad. Med. **21**:3 (Jan.) 1945; Am. J. Syph., Gonor. & Ven. Dis. **29**:185 (March) 1945.

in estimating results is the comparative incidence of relapse, clinical or serologic. With a total dose of 60,000 units in seven and one-half days, the eventual early relapse rate is indicated 100 per cent; with 1,200,000 units, about 15 to 20 per cent. A large series of patients have now been treated with 2,400,000 and 3,600,000 units in seven and one-half days, and are now under observation. The time elapsed is too short to permit definite comparisons. Under simultaneous study is the variable of time. Halving the duration of treatment is not helpful; whether doubling it to e.g., fifteen days improves the situation is a problem for future study. Finally, in early syphilis there is some suggestion that penicillin in combination with an arsenoxide may be more effective than either drug alone. So much for uncomplicated early syphilis. Simultaneously it has been shown that penicillin is apparently completely effective in early syphilis resistant to arsenic and bismuth; it appears to be of great value in the prevention of congenital syphilis in infants born of recently infected mothers; it produces dramatically favorable effects in early neurosyphilis, and it is useful in infantile congenital syphilis. Resistance to penicillin has not been encountered. Late syphilis of various types presents a much more complex problem, which will require many years of study.

As matters stand at present, penicillin is a new and powerful addition to syphilotherapy. How best to use it, alone or in combination with other forms of treatment, is as yet undetermined.

Early Syphilis.—Neilson and his associates [86] report preliminary but not particularly informative results of the penicillin treatment of 63 adults and 12 infants (9 with congenital infections) with early syphilis. All of the first group were treated with a total dose of 2,400,000 units of penicillin and were said to have had "adequate" follow-up and observation, although this period of time is not otherwise defined. The results of treatment were good in all but 11 of the 63 adults. In 8 no appreciable fall in serologic titer occurred following treatment; and in 3 patients infectious relapse lesions developed. The initial results in the group of 12 babies and children are described as equally good.

Binkley and Kile [87] were assigned by the Penicillin Panel the following schedules for the treatment of early syphilis positive on dark field examination: (a) 1,000 units of penicillin to be given every three

86. Neilson, A. W.; Chard, F. H.; Hanchett, L. J.; Ayers, E.; Stepita, C. T., and Rodriquez, J.: Penicillin in the Treatment of Syphilis and Gonorrhea, South. M. J. **38**:204 (March) 1945.

87. Binkley, G. W., and Kile, R. L.: Rapid Treatment of Early Syphilis with Small Doses of Penicillin: Observations in One Hundred and Fifty-Nine Cases, Arch. Dermat. & Syph. **51**:200 (March) 1945.

hours over seven and one-half days (total dose 60,000 units); (*b*) this same schedule plus oxophenarsine hydrochloride, 40 mg. daily for a total of 320 mg.; (*c*) 5,000 units of penicillin every three hours for a total dose of 300,000 units in seven and one-half days. A total of 159 patients were treated. The relapse rate (all types) in these three series of patients after periods of observation ranging from six to ten months was, respectively: series (*a*), 81 per cent; series (*b*), 60 per cent; series (*c*), 45 per cent. On the other hand, 7 of 10 patients treated with 1,200,000 units in seven and one-half days were clinically and serologically well at the end of one year. The small dosage schedules originally assigned to these workers are obviously inadequate.

Ross and his associates [88] devote considerable space to treatment with penicillin of 5 patients with secondary syphilis, using either 1,200,000 units administered hourly for forty injections in a total of forty hours or 2,400,000 units given every three hours for eighty injections within ten days. The results were unsatisfactory in 3 of the 5 patients.

Norcross [89] has treated 110 patients with primary and 44 with secondary syphilis with the current Army system of 2,400,000 units, given in sixty intramuscular injections of 40,000 units each every three hours in a total of seven and one-half days. The results presented are immediate only, dealing with disappearance of spirochetes and healing of lesions. In these respects, Norcross thinks that the therapeutic response of early syphilis to penicillin is not so rapid as that to oxophenarsine hydrochloride. Incidentally, he also observed that the administration of 1,800,000 to 5,400,000 units of penicillin to 25 non-syphilitic persons did not produce any biologic false positive reactions to serologic tests.

Nelson and Duncan [90] present the immediate result of penicillin treatment of 6 patients with treatment-resistant early syphilis. All the patients had psoriasiform lesions in which, with one exception, T. pallidum was demonstrated by dark field examination. In each instance the lesions had appeared while the patients were under treatment with adequate amounts of trivalent arsenicals, usually combined with bismuth. Varying dosage schedules of penicillin were employed, ranging from a total dose of 60,000 to one of 2,000,000 Oxford units. In all but

88. Ross, A. O. F.; Nelson, R. B.; Lourie, E. M., and Collier, H. O. J.: Treatment of Early Syphilis with Penicillin, Lancet **2**:845 (Dec. 30) 1944.

89. Norcross, B. M.: Observations on Treatment of Early Syphilis with Penicillin, M. Bull. North African Theat. Op. **2**:110 (Nov.) 1944.

90. Nelson, R. A., and Duncan, L.: Penicillin in the Treatment of Early Syphilis Resistant to Arsenic and Bismuth, Am. J. Syph., Gonor. & Ven. Dis. **29**:1 (Jan.) 1945.

1 of the patients the lesions healed promptly, and the serologic trend up to the time of this report was favorable. The mucosal lesions of 1 patient persisted after a total dose of 60,000 units but healed promptly after a subsequent course of 1,200,000 units. On the basis of their experience and the available information to date, the authors recommend a total dosage of not less than 2,400,000 units of penicillin for patients with syphilis resistant to arsenic and bismuth.

McDermott and his co-workers [91] discuss the time-dosage relationship of penicillin therapy as it applies to early syphilis. They summarize as follows:

Observations of the action of penicillin on infectious syphilis suggest that only short periods of penicillin action are necessary for the immediate destruction of a large number of the organisms, but prolonged penicillin action is necessary for cure. In addition, there is some evidence that *in vivo*, as with bacterial cultures *in vitro*, large increases in the concentration of penicillin for short periods do not shorten this period of time necessary for cure.

Analysis of the regimens under investigation for the treatment of early syphilis reveals that in any given system, regardless of the total amount of penicillin or the number of days of treatment, there is a wide variation in the total period of time during which detectable concentrations of penicillin are present in the serum, depending upon the timing and size of the individual doses.

As both studies *in vitro* and clinical experience lend support to the thesis that *it is not the production of multiple peaks of high concentrations of penicillin but the length of the action at low concentrations which is the important factor,*[92] it is suggested that this penicillin action-time be given consideration in the planning of new regimens for the treatment of syphilis. In calculations involving the use of penicillin in beeswax and other inhibitors of absorption, this time of action of the penicillin is the only available index for comparison with the other systems.

There is a possibility, as indicated by *in vitro* experiments, that once the initial effect of the penicillin action has occurred, subsequent action need not be absolutely continuous to obtain the maximum effect.

Using a serum concentration of 0.078 unit of penicillin as an arbitrary standard, a number of regimens (presented in tabular form) have been calculated which would produce this concentration, for total periods of 90, 120 and 160 hours by a minimum of intramuscular injections.

Acute Syphilitic Meningitis.—Nelson and Duncan [93] present a preliminary report of the effect of penicillin on acute syphilitic meningitis in 10 patients. The route of administration was intramuscular. The clinical manifestations in these patients were typical of acute syphilitic meningitis in all, including headache (all patients), stiff neck (3 patients), cranial nerve palsies (5 patients), papilledema (2 patients),

91. McDermott, W.; Benoit, M., and DuBois, R.: Time-Dose Relationships of Penicillin Therapy: III. Regimens Used in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **29:**345 (May) 1945.

92. The italics are ours. Compare the quotation from Dale in an earlier section.

93. Nelson, R. A., and Duncan, L.: Acute Syphilitic Meningitis Treated with Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **29:**141 (March) 1945.

convulsions, drowsiness and stupor (2 patients); and the laboratory observations were confirmatory. The dose of penicillin employed ranged from 600,000 to 4,000,000 units; the duration of treatment was seven and one-half to eleven days. These dose and time intervals are not suggested as the optimum. The effectiveness of intramuscular treatment in early neurosyphilis and the lack of necessity for use of the intrathecal route are borne out by the results presented.

The patients have been followed for one hundred and four to three hundred and ten days, and no clinical relapses have been observed. The immediate symptomatic result was dramatically favorable in all cases. The effect on the spinal fluid was equally pronounced. The original cell counts before treatment varied from 42 to 1,450. At the last observation, cell counts were normal in 8 of the 10 patients, almost normal in 1 and still considerably elevated (relapse) in 1. The protein content of the spinal fluid likewise showed a definite downward trend. The quantitative Wassermann reaction of the spinal fluid, originally positive in all patients in varying dilutions, has shown improvement in all patients, and reversed to negative in 5 of the 10. The collodial mastic curve has likewise improved. Nelson and Duncan point out that in spite of the observations cited here, it is believed on the basis of the results accumulating in uncomplicated early syphilis, that patients with acute syphilitic meningitis should receive a total of 2,000,000 to 3,000,000 Oxford units of penicillin administered by the intramuscular route every three to four hours day and night, over a minimum period of eight to sixteen days.

Goldman [94] has treated 19 patients with dementia paralytica (18 referred to in the text, 19 in the tables). Eleven of the 18 paretic patients were treated with a combination of intrathecal and intramuscular injections. Six intrathecal injections were given at daily intervals, the first two of 10,000 units and the subsequent four of 20,000 units each, i.e., a total of 100,000 units. In addition, a total of 800,000 units of penicillin was administered intramuscularly during the six days of intrathecal injections. One month later a second series, totaling 1,000,000 units of intramuscular injections alone, was given. Eight patients had fever on one or more days following the intrathecal injection. Pleocytosis in the spinal fluid was observed in "almost every instance." Aside from these, no serious local manifestations from intrathecal treatment were observed. Two of these 11 patients died within ten days following the first series of treatment. Their condition, however, was thought to be very poor before treatment. Of the

94. Goldman, D.: Treatment of Neurosyphilis with Penicillin: A Preliminary Report, J. A. M. A. **128**:274 (May 26) 1945.

remaining 9 patients, 3 are said to have completely recovered, 3 much improved and the remaining 3 somewhat improved.

A second group of patients (7) with dementia paralytica was treated with a combination of artificial fever (the author says three fever sessions given once weekly for a period of four weeks [sic] to a total of approximately thirty hours of temperature over 105 F.) and penicillin. After the third or fourth [sic] fever treatment, a course of 1,000,000 units of penicillin was given, and a month later another course of 1,000,000 units, without further fever treatment. Of these 7 patients, 2 are said to be completely recovered, 3 much improved and 2 somewhat improved. The author provides no information as to the length of time for which these patients have been followed after treatment and no data as to serologic outcome.

He has also treated 4 patients with tabes dorsalis. 2 of whom had "tabetic crises with pronounced abdominal and other sensory root symptoms." The other 2 had "typical motor manifestations of ataxia of the lower extremities." These 4 patients were treated with penicillin intrathecally only, to a total of 100,000 units given in six daily injections. One of them was subsequently treated with a pentavalent arsenical. The 2 with crises showed "improvement that was almost immediate and is apparently of an enduring nature." There is again no statement as to the length of the observation period, so that "enduring" is perhaps a strong word.

The chief importance of Goldman's paper lies in the fact that he administered a large number of intrathecal injections in doses not exceeding 20,000 units without producing any serious neurologic reactions.

Neymann, Heilbrunn and Youmans,[95] confirming the observations of others that penicillin cannot be demonstrated in the cerebrospinal fluid after its intravenous or intramuscular administration, experimented with the intracisternal administration of the drug to 3 patients. To these 3, single intracisternal injections of 30,000 units each were administered daily for two weeks. Apparently, though one cannot be sure from the cloudy language of the authors, all of these 3 patients had either "acute" or "chronic" reactions, the manifestations of which (headache, "tenseness," muscular twitchings, severe convulsions, stiff neck, pleocytosis, fever, coma) seem to be essentially identical, and 2 of the 3 died ten days after the last intracisternal injection.

These 3 patients apparently form part of a series of 5 patients with dementia paralytica treated by the authors. Eight different methods

95. Neymann, C. A.; Heilbrunn, G., and Youmans, G. P.: Experiments in the Treatment of Dementia Paralytica with Penicillin, J. A. M. A. **128**:433 (June 9) 1945.

of administration of the drug, alone or in combination with other agents, were tried, but it is impossible to determine from the article which method or methods were employed in the individual cases, how much treatment was given or for how long the patients were followed. Three of the 5 patients are dead, 2 from the reactions to treatment described earlier and 1 from "exhaustion," two weeks after treatment. One is improved; the other is unchanged.

The article is worthless as an index of the value of penicillin in neurosyphilis. . Its only value lies in the demonstration that the frequent intrathecal injection of such large doses of penicillin as 30,000 to 100,000 units is fraught with great danger.

Emphasizing the local toxicity of penicillin utilized intrathecally, Johnson and Walker [96] report the case of a 22 month old child with an obscure febrile illness of the nervous system, to whom 50,000 units of penicillin was given intraventricularly in 5 cc. of isotonic solution of sodium chloride. One hour later the child went into collapse and was unconscious, with unobtainable blood pressure and with stiffness of the neck. Three hours later a generalized convulsion occurred, which continued with increasing intensity for an hour. Eight hours after the injection, however, the child seemed well. Four days after the first injection, further intraventricular injections were begun, this time with 15,000 units each, and continued twice daily for four additional doses without serious difficulty. This case stimulated Walker and Johnson [97] to further experimental investigation of the possibility of direct damage to the brain by penicillin. The intracortical injection of small amounts of penicillin in cats and monkeys may result in convulsive seizures or death due to circulatory collapse. Powdered penicillin applied locally to the undamaged arachnoid of monkeys, cats and human beings produces clinical and electroencephalographic manifestations of convulsions. On the basis of the reported case and their later animal experimentation, the authors suggest that penicillin should not be used intraventricularly unless absolutely necessary, and then only in small amounts and with caution. This and further similar but as yet unpublished studies are of major importance with respect to the possible intrathecal injection of penicillin by any route (intraventricular, intracisternal, intraspinal) for neurosyphilis.

Hindle and his co-workers [98] report that during investigations on the use of penicillin in neurosyphilis, 28 patients received both penicillin

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96. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: A Note of Warning, J. A. M. A. **127**:217 (Jan. 27) 1945.

97. Walker, A. E., and Johnson, H. C.: The Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69 (Feb.) 1945.

(Footnotes continued on next page)

and benign tertian malaria. Fifteen of these had penicillin administered simultaneously with the malaria. Hindle and his colleagues demonstrated that penicillin does not suppress fever or the parasite count of active inoculation malaria and that when given before or at the time of the malaria inoculation it does not prevent or postpone the development of fever and parsitemia. This is an advantage to the treatment of neurosyphilis, since both malaria and penicillin can be given simultaneously.

Stokes and his co-workers [99] discuss what is known. and what one wants to know regarding penicillin therapy of late syphilis, especially neurosyphilis. Several illustrative cases are presented in this paper.

Prevention and Treatment of Prenatal Syphilis.—Lentz and his associates [100] have studied 12 pregnant women with early and 2 with early latent syphilis, and 9 infants with early congenital syphilis, all treated with penicillin. None of these patients had received previous antisyphilitic treatment. The authors conclude as follows:

1. There are several factors in the medical treatment of the syphilitic pregnant woman and the infant with congenital syphilis which are in need of further study and improvement.

2. It was with the thought that some solution to these problems might be found through the use of penicillin that the present study was undertaken. Sodium penicillin exclusively was employed. Experience with the treatment of 14 pregnant women with early syphilis and 9 infants with congenital syphilis formed the basis for this analysis.

3. The material is reported at this time, even though incomplete, since preliminary observations indicate that sodium penicillin has a definitely good effect both on the mother and on the child in syphilis in pregnancy and on infantile congenital syphilis. Because the drug has been released for general distribution, dissemination of even our present limited knowledge seems desirable.

4. The proper total dosage and the time-dose relationship has not been worked out to complete satisfaction either for syphilis and pregnancy or for infantile congenital syphilis.   .

5. The limited existing data would seem to indicate, however, that total doses of the magnitude of 1,200,000 Oxford units and 2,400,000 Oxford units given intramuscularly round the clock in approximately eight days, as used·in the treatment of early syphilis, are well tolerated by the pregnant woman, with the possible

98. Hindle, J. A.; Rose, A. S.; Trevett, L. D., and Prout, C.: The Effect of Penicillin on Inoculation Malaria: A Negative Report, New England J. Med. **232**:133 (Feb. 1) 1945.

99. Stokes, J. H.; Beerman, H.; Ingraham, N. R., Jr.; Lentz, J. W.; Morgan, H. G.; Gammon, G. D.; Steele, W.; Rose, E. K., and György, P.: Penicillin in Late Syphilis: An Interim Report, Am. J. Syph. Gonor. & Ven. Dis. **29**:313 (May) 1945.

100. Lentz, J. W.; Ingraham, N. R., Jr.; Beerman, H., and Stokes, J. H.: . Penicillin in the Prevention and Treatment of Congenital Syphilis: Report on Experience with the Treatment of Fourteen Pregnant Women with Early Syphilis and Nine Infants with Congenital Syphilis, J. A. M. A. **126**:408 (Oct. 14) 1944.

exception that therapeutic or placental shock may occur, to be avoided by considerably reducing the dose for the first thirty-six to forty-eight hours of therapy. The course of expert experience with penicillin in syphilis in general suggests the desirability of the higher dosage (2,400,000 Oxford units).

6. Preliminary results indicate that "cure" or suppression of the infection takes place in a number of the mothers and that miscarriage, stillbirth and neonatal death are averted and the infants are born apparently healthy. It must be reiterated, however, that the period of observation for either mother or child has not been long enough to be certain that they have been cured by the dosages employed. The course of the disease has nonetheless been profoundly and favorably affected.

7. Infants with congenital syphilis make a good response to dosage of approximately 18,000 units per pound of body weight. Grossly infected syphilitic infants, however, may be injured by the injudicious use of penicillin. In the present state of our knowledge their treatment should be approached with extreme caution, with reduced dosage and with great emphasis on proper general pediatric care.

Platou and his co-workers [101] present a brief preliminary note concerning 69 infants with manifest early congenital syphilis who have been treated with sodium penicillin by the university groups at Baltimore, Philadelphia, Galveston and New Orleans. Penicillin was administered intramuscularly in isotonic solution of sodium chloride every three hours in sixty injections over a seven and one-half day period. Total doses used ranged from 16,000 to 32,000 Oxford units per kilogram of body weight. No other antisyphilitic treatment was given.

In 34 of these 69 infants reactions occurred during treatment. Nearly all were mild, consisting of moderate fever beginning on the first or second day of treatment and seldom lasting longer than three days. One infant, forty-eight hours after treatment was begun, suddenly had a severe, nearly fatal collapse. Three infants died during or soon after treatment (twenty-four hours, seven days and nine days, respectively, after penicillin was started); all of these had active syphilitic lesions, were under 2 months of age and were in poor general condition. Two other infants died five weeks and fourteen weeks after receiving penicillin; whether the latter deaths were directly or indirectly due to penicillin or syphilis is not known.

In general, the immediate response of early congenital syphilis to penicillin has been gratifying. Cutaneous and mucosal lesions have healed; rhinitis has been somewhat more persistent, healing in from two weeks to two months. Roentgenographic evidence of osteitis disappeared in two to six months. Regression of hepatic, splenic and lymph node enlargement, though variable, was usually complete by three months. If abnormal spinal fluid findings were present initially, these have returned to normal in all cases in from eight days to six months.

101. Platou, R. V.; Hill, A. J.; Ingraham, N. R.; Goodwin, M. S.; Wilkinson, E. E., and Hansen, A. E.: Penicillin in the Treatment of Infantile Congenital Syphilis: A Brief Preliminary Note, J. A. M. A. **127**:582 (March 10) 1945.

Of the 69 infants, 39 have been followed for four to twelve months. Twenty-five of these 39 now are physically normal and show doubtful or negative reactions to serologic tests (21 negative, 4 doubtful). Serologic relapse has occurred in 5 infants, and clinical relapse in 2 of these 5.

The dosage schedules so far employed have corresponded to a total dose of 1,000,000 to 2,000,000 units in seven and one-half days for an adult with early acquired syphilis.

The results obtained to date in infants indicate that the present total dose and time-dose relationship are not entirely satisfactory. For the present, Platou's group believes that an increase in total dose with the same time-dose relationship should be tried first. Accordingly, they recommend temporarily a total dose of 40,000 Oxford units per kilogram of body weight given in sixty intramuscular injections over a seven and one-half day period. Attention is called to the vital necessity of adequate supportive care of acutely ill infants.

Diffusion of Penicillin Through the Placenta.—The problem of diffusion of penicillin from the maternal to the fetal circulation was apparently first studied by Herrell, Nichols and Heilman.[102] They administered 100,000 units intravenously to the mother toward the end of the second stage of labor. At delivery, or shortly after, blood was obtained from the mother and from the fetal cord for determination of penicillin levels in the blood. The drug was constantly present in the fetal circulation, in concentrations ranging from about one-eighth to one-half of that present in the mother's blood.

This observation has been confirmed by Hutter and Parks [103] and by Greene and Hobby.[104] Hutter and Parks [103] administered penicillin to pregnant women at intervals ranging from twenty-five to one hundred and five minutes before delivery. A dose of 20,000 units to 1 patient and of 40,000 units to 2 patients resulted in concentrations of less than 0.02 unit per cubic centimeter in the infant cord blood. When 100,000 units were administered intramuscularly to the mother, levels ranging from 0.02 to 0.2 units per cubic centimeter were obtained in the fetal cord blood. These concentrations of penicillin are approximately one fifth as great as the concentrations in the maternal blood at the moment of delivery. There are no data on the passage of penicillin through the placenta during the first and second trimesters of pregnancy.

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102. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with an Analysis of One Hundred and Fifty Cases in Which It Was Employed, J. A. M. A. **125**:1003 (Aug. 12) 1944.

103. Hutter, A. M., and Parks, J.: The Transmission of Penicillin Through the Placenta: A Preliminary Report, Am. J. Obst. & Gynec. **49**:663 (May) 1945.

104. Greene, H. J., and Hobby, G. L.: The Transmission of Penicillin Through the Human Placenta, Proc. Soc. Exper. Biol. & Med. **57**:282 (Nov.) 1944.

Greene and Hobby [104] have also demonstrated the transmission of penicillin through the human placenta. Penicillin was adminstered intravenously to 4 normal patients in active labor. In 2 instances in which the mother received 100,000 units both maternal blood and fetal cord blood showed significant amounts of penicillin within two hours after administration. Another patient received 20,000 units one hour before delivery; penicillin was demonstrated in the maternal but not in the fetal cord blood. In another patient who also received a similar amount of penicillin and who delivered one-half hour later penicillin was demonstrated in the maternal and fetal cord blood but not in the amniotic fluid.

The fact that penicillin passes from the maternal into the fetal circulation in effective concentrations suggests a wide therapeutic application of a relatively nontoxic agent for the control of penicillin-susceptible infections which affect both mother and her unborn infant. Of these infections syphilis should receive greatest consideration.

The Masking of Syphilis by Small Doses of Penicillin.—That penicillin administered for the treatment of gonococcal infection might mask or alter the subsequent development of manifestations of concomitantly acquired early syphilis has been generally recognized since Mahoney's discovery of the efficacy of this antibiotic in the treatment of early syphilis. Reports are now beginning to appear substantiating this hypothesis. Ricchiuti [105] presents two such reports. One patient with gonorrhea and balanitis was treated with 100,000 units of penicillin. This was accompanied by an elevation of temperature to 101.4 F., which in restrospect was undoubtedly a Herxheimer reaction. A dorsal slit, subsequently performed, revealed an indurated lesion in the coronal sulcus repeated dark field examinations of which failed to demonstrate T. pallidum. Sixteen days later reactions to serologic tests for syphilis became positive, the penile lesion had healed, and there were not any manifestations of secondary syphilis. A second patient received penicillin (100,000 units) for gonorrhea prior to the development of a penile sore, a time at which specimens appeared persistently free from T. pallidum when subjected to dark field examination. Later, generalized lymphadenopathy occurred, but reactions to blood serologic tests remained negative during an eight week period of observation. The diagnosis of syphilis in this instance could not be made.

Boyd, Wagner and Hewson [106] report the case history of a patient who received 80,000 units of penicillin for gonococcic epididymitis.

105. Ricchiuti, J. F.: Penicillin Therapy in Gonorrhea with Associated Undiagnosed Early Syphilis, U. S. Nav. M. Bull. 43:1031 (Nov.) 1944.

106. Boyd, G. G.; Wagner, J. A., and Hewson, G. F.: Effects of Subtherapeutic Dose of Penicillin on Development of Primary Syphilitic Lesions, U. S. Nav. M. Bull 43:1034 (Nov.) 1944.

Sixty days after his last sexual exposure (approximately thirty days after penicillin therapy) a penile lesion developed, which subsequently was proved to be syphilitic. The authors suggest that the penicillin therapy for gonorrhea resulted in a prolonged incubation period for primary syphilis.

Steinberg and Immergut [107] add 3 more case reports to the literature. In the first instance the patient received 125,000 units of penicillin for gonococcal urethritis. Five weeks later, not having been sexually exposed in the interim, the patient reappeared with a genital lesion which was syphilitic on dark field examination. In the second instance the patient received a similar amount of penicillin for gonorrhea. A genital lesion present at that time was inadvertently not subjected to dark field examination until one week later. Repeated dark field examinations then gave negative results for syphilis, as did blood tests, until ten days after the penicillin therapy for gonorrhea. At that time blood tests gave doubtful and later increasingly more positive reactions. The third patient received 125,000 units of penicillin for gonococcic cervicitis. Then and during the subsequent two weeks examinations for syphilis gave negative results. Seven weeks after penicillin therapy the patient returned with a secondary cutaneous rash but with no evidence of a preexisting primary lesion.

Other similar cases have been recorded by Van Slyke and Steinberg,[108] Carpenter,[109] Shafer and Zakon,[110] Hailey,[111] Baier and Pincus [112] and perhaps others, and attention has been drawn to the danger in many papers dealing with the use of penicillin in both gonorrhea and syphilis. The United States Army has dealt with the problem by requiring serologic tests of the blood for syphilis as follow-up after the treatment of gonorrhea with penicillin, the last one not earlier than four months after treatment. This should be sound civilian practice.

107. Steinberg, S., and Immergut, S.: Diagnosis of Early Syphilis Masked or Delayed by Penicillin Therapy of Gonorrhea, Urol. & Cutan. Rev. **49**:175 (March) 1945.

108. Van Slyke, C. J., and Steinberg, S.: Outpatient Penicillin Treatment of Gonococcic Infections in Males, Ven. Dis. Inform. **25**:229 (Aug.) 1944; Outpatient Penicillin Therapy of Gonorrhea in Men, ibid. **26**:1 (Jan.) 1945.

109. Carpenter, C. C.: Failure of Penicillin to Prevent Syphilis, U. S. Nav. M. Bull. **43**:389 (Aug.) 1944.

110. Shafer, B., and Zakon, S. J.: Early Syphilis Masked and Delayed by Penicillin in the Treatment of Gonorrhea, Arch. Dermat. & Syph. **50**:200 (Sept.) 1944.

111. Hailey, H. E.: Suppression of Syphilis by Penicillin Therapy of Gonorrhea, Arch. Dermat. & Syph. **50**:269 (Oct.) 1944.

112. Baier, G. F., III, and Pincus, J. A.: The Effect of a Small Dose of Penicillin on the Diagnosis of Early Syphilis, Mil. Surgeon **95**:359 (Nov.) 1944.

Penicillin in Mixed Chancroidal and Syphilitic Infections.—Pereyra and Landy [113] point out that penicillin is ineffective in the treatment of chancroidal infections in man, a point of importance in mixed infections with chancroid and syphilis. Failure of a chancre to heal under treatment with penicillin may occur under these conditions, and supplementary treatment with sulfonamide drugs may be necessary.

Asthma as a Reaction to Penicillin.—Price and his associates [114] report a serious reaction occurring in a white man, aged 24, with early syphilis, to whom was given 2,400,000 units of penicillin divided into sixty doses of 40,000 units each, administered intramuscularly every three hours in seven and one-half days. Two days after the completion of this treatment asthma, giant urticaria, fever and malaise developed. There was a remarkable association between the height of the fever and the intensity of urticaria and asthma. Three days after the onset of this reaction the patient had a very severe asthmatic attack in which he became comatose and his rectal temperature rose to 105 F. The entire episode ended in four to five days in complete recovery. Sensitivity of the skin to penicillin could not be demonstrated in this patient.

New Books Dealing with Penicillin in Syphilis.—The third edition of "Modern Clinical Syphilology," now for the first time under the joint authorship of Stokes, Beerman and Ingraham,[115] has just appeared. It is, as it has been in the two preceding editions, the outstanding contribution in English or in any other language in the general field of syphilology. The final chapter is devoted to penicillin. It is inescapable that at this time many of the statements in this chapter must be regarded as provisional, subject to immediate and perhaps drastic revision. For a statement of current knowledge as of the time of writing (September 1944), and particularly the gaps in present knowledge, it cannot be too highly commended. Figures 897 (A General Statement of Facts) and 898 (The Known and the Unknown) from this text provide in brief form an excellent summary of knowledge about the use of penicillin in cases of syphilis as of the late summer of 1944.

Herrell's [116] three hundred and forty-eight page monograph, "Penicillin and Other Antibiotic Agents," provides a useful general summary

113. Pereyra, A., and Landy, S.: Experimental Prophylaxis and Treatment of Chancroidal Infection: Inefficacy of Penicillin Administered Intramuscularly, U. S. Nav. M. Bull. **43**:189 (July) 1944.

114. Price, D. E.; McNairy, D. J., and White, E. L.: Severe Asthma: Delayed Sensitization to Penicillin, J. A. M. A. **128**:183 (May 19) 1945.

115. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Modern Clinical Syphilology, ed. 3, Philadelphia, W. B. Saunders Company, 1944.

116. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, W. B. Saunders Company, 1945.

of the present status of penicillin. Of special interest to the syphilotherapeutist are the chapters on the physical and chemical properties of the drug; on its absorption, diffusion and excretion and on its clinical use in syphilis (Chapter XVII). The last-named chapter includes a summary of the scanty available literature (to April 1945). The criticism may be offered that definite plans of treatment for various stages of syphilis are proposed, though there is as yet no definite evidence that the plans suggested are of maximum effectiveness or even that at least one of them (e. g., for neurosyphilis, 20,000 units of penicillin administered intrathecally every forty-eight hours during the period of systemic therapy) is safe. Although the absorption-delaying method of administration of penicillin in peanut oil–beeswax (Romansky and Rittman) is described, its possible applicability in the treatment of syphilis is not discussed.

Kolmer [117] has likewise summarized available current knowledge concerning penicillin in a small monographic presentation of three hundred and two pages. This book also includes the basic information on the physical and chemical properties of the drug, its action and toxicity, the administration of a dosage and a twenty page chapter on the use of the drug in syphilis. Kolmer, recognizing the preliminary nature of the so far published information, refrains from offering definite plans of treatment for various types of syphilis, contenting himself with a careful review of the reports of others.

CARDIOVASCULAR SYPHILIS

Incidence.—An excellent opportunity to determine the incidence of cardiovascular syphilis in the younger age group has been afforded by selective service examinations. Flaxman [118] recorded the incidence of cardiac history and findings among 23,000 inductees and volunteers examined in Chicago from February 1943 to June 1944. Of the entire group, only 3 were found to have syphilitic aortic insufficiency. There is no recorded incidence of an aneurysm; uncomplicated syphilitic aortitis was unmentioned. Therefore only 0.0013 per cent of the entire group were found by Flaxman to have syphilitic heart disease. There were 203 (12.4 per cent of the men with a history of the physical findings of cardiac disease) with rheumatic heart disease, and it is of interest to note that 15 of these (7.4 per cent) had rheumatic lesions of the aortic valve only.

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117. Kolmer, J. A.: Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy, New York, D. Appleton-Century Company, Inc., 1945.

118. Flaxman, N.: Initial Cardiac Examination of Twenty-Three Thousand Inductees and Volunteers, Am. J. M. Sc. **209**:657 (May) 1945.

Syphilitic Aortitis.—Jackman and Lubert[119] think that syphilitic aortitis is a much more frequent cause of calcification in the aortic wall than is aortic atherosclerosis. This opinion is based on roentgenographic evidence of aortic calcification in 22.7 per cent of 66 patients, averaging 57 years in age, subsequently proved to have syphilitic aortitis, as contrasted with similar roentgenographic evidence in only 3.2 per cent of 62 patients, averaging 70 years in age, with anatomically proved cases of severe sclerosis of the thoracic aorta. On the other hand, Blumenthal, Lansing and Wheeler,[120] who studied pathologic sections from 582 aortas, think that age and hypertension are more important factors than syphilis in the production of calcium deposits.

Differential Arterial Blood Pressure in Aortic Regurgitation.—The commonly used clinical methods of measuring arterial blood pressure are based on the concepts proposed by the original workers, remark Kotte, Iglauer and McGuire.[121] Examination of these early publications reveals that their technics are founded on indirect evidence. The usual clinical concept is that the femoral systolic blood pressure is approximately equal to that in the brachial artery in normal persons but that in aortic insufficiency and under certain other conditions it is considerably higher.

In the present study blood pressure was measured in the brachial and femoral arteries of subjects with normal pressures, hypertension and aortic insufficiency by cuff methods and by use of the direct method (a small needle is inserted into the artery and blood pressure readings are measured by a specially designed instrument, an optical manometer). It was desired, first, to test the accuracy of the 15 cm. cuff for measure-ments of blood pressure in the thigh; second, to test the validity of the impression that aortic regurgitation produces a disproportionate elevation of the systolic pressure in the leg, and, third, to compare the respective femoral pressures with the concomitant pressures in the arms.

Measurements were made on 9 patients with normal blood pressures, 9 with hypertensive cardiovascular disease and 10 with aortic insufficiency. The ordinary arm cuff (13 cm. in width) was used for the arm, and the same cuff and, in addition, a wider cuff (15.5 cm.) were used for

119. Jackman, J., and ·Lubert, M.: The Significance of Calcification in the Ascending Aorta as Observed Roentgenologically, Am. J. Roentgenol. **53**:432 (May) 1945.

120. Blumenthal, H. T.; Lansing, A. I., and Wheeler, P. A.: Calcification of the Media of the Human Aorta and Its Relation to Intimal Arteriosclerosis, Ageing and Disease, Am. J. Path. **20**:665 (July) 1944.

121. Kotte, J. H.; Iglauer, A., and McGuire, J.: Measurements of Arterial Blood Pressure in the Arm and Leg: Comparison of Sphygmomanometric and Direct Intra-Arterial Pressures, with Special Attention to Their Relationship in Aortic Regurgitation, Am. Heart J. **28**:476 (Oct.) 1944.

measurements of the femoral pressures. The cuff pressures in the arm varied both above and below the direct values. The error was slight for the systolic level, averaging + 0.5 per cent, but reached more sizable proportions with the diastolic pressures of the normotensive and hypertensive groups, in which it was of the order of + 9 per cent. · The cuff error for diastotic pressures was even greater in subjects with aortic regurgitation, averaging + 24 per cent. The 15.5 cm. cuff permitted a much more accurate measurement of the femoral pressures than did the 13 cm. cuff. With the 15.5 cm. cuff the average error in the normotensive and hypertensive groups was + 2.6 per cent and + 8 per cent, respectively. In this instance the error in the results for the diastolic pressure averaged + 25 per cent for the combined groups. The systolic and diastolic values with the wide cuff on the thigh were most in error in subjects with aortic regurgitation (averaging + 29 per cent and + 67 per cent, respectively). The femoral systolic blood pressure was notably higher than the direct brachial systolic pressure in 5 of the 9 normotensive subjects, 4 of the 9 hypertensive and 7 of the 10 patients with aortic regurgitation. It is pointed out that the femoral systolic pressure was more frequently elevated in the patients with aortic regurgitation and that the differences were usually greater in these subjects than in the control and hypertensive groups.

Kotte and his colleagues conclude that the systolic blood pressure in the arm can be measured with reasonable accuracy in subjects with normal pressure, hypertension and aortic regurgitation by the ordinary arm cuff and auscultatory technic. The brachial diastolic pressure as measured by the cuff is usually too high, especially in aortic regurgitation. The femoral systolic blood pressure cannot be measured accurately with the 13 cm. cuff, but the 15.5 cm. cuff permits more accurate measurements in all except subjects with aortic regurgitation, whose pressures cannot be measured accurately with either cuff. Femoral diastolic pressures obtained with either cuff were grossly inaccurate in all subjects.

Finally, the difference between the blood pressure in the arm and that in the leg in patients with aortic regurgitation is not so pronounced as is generally believed because the cuff, wide or narrow, does not allow true measurements of femoral pressure. Therefore it is probable that no diagnostic value should be attributed to the differential blood pressure.

Abdominal Aneurysms.—The overwhelming role of syphilis in the causation of aneurysms of the thoracic aorta has been repeatedly and conclusively demonstrated. Aneurysms of the abdominal aorta have been less thoroughly studied. Scott [122] finds that, although more than

122. Scott, V.: Abdominal Aneurysms: A Report of Ninety-Six Cases, Am. J. Syph., Gonor. & Ven. Dis. **28**:682 (Nov.) 1944.

500 cases are reported in the literature, many publications antedate both the discovery of the Wassermann reaction and the general recognition of the specific histopathology of syphilitic aortitis. He summarizes his own study as follows:

1. The etiology of abdominal aneurysm (aorta and branches) in 96 patients was as follows: syphilis 58.3 per cent, arteriosclerosis 20.0 per·cent, bacterial agents (mycotic) 18.8 per cent, periarteritis nodosa 1.0 per cent, and tuberculosis by direct extension 1 per cent.

2. Sixty-two patients had aneurysms of the abdominal aorta of which 74 per cent were syphilitic, 21 per cent arteriosclerotic, and 5 per cent mycotic.

3. Of 43 patients with aneurysms of branches of the abdominal aorta, 35 per cent were due to syphilis, 18.6 per cent to arteriosclerosis, 41.9 per cent to bacterial agents. Tuberculosis and periarteritis caused aneurysm in one patient each.

4. Multiple abdominal·aneurysms were present in 18.7 per cent of the patients (14.4 per cent of the syphilitic group, 30 per cent of the arteriosclerotic, 16.5 per cent of the mycotic).

5. Syphilis is the major cause of aneurysms of the upper abdominal aorta and of aneurysms arising at the origin of the major upper branches (celiac axis and superior mesenteric artery). Aneurysms of the lower aorta and of other branches are rarely syphilitic; instead, they are arteriosclerotic (aorta), or mycotic (smaller branches).

6. Of the syphilitic aneurysms, 75 per cent occurred in patients under 50 years of age, and 98 per cent under age 60. All the arteriosclerotic aneurysms occurred in patients over 50, and 70 per cent were in the age group over 60. The highest incidence of mycotic aneurysms was in the younger age groups.

7. The incidence of syphilitic aneurysms was highest in the colored race (64 per cent) and in the male sex (89 per cent). Arteriosclerotic aneurysms in this series were limited to patients of the white race and 85 per cent occurred in males.

8. The symptomatology of abdominal aneurysm is variable because of differences in location and size. In the syphilitic group the most significant symptom was pain (abdominal or back) present in 84 per cent. This was characteristically most severe at night and relieved by change of position. The majority (80 per cent) of arteriosclerotic aneurysms were asymptomatic.

9. The presence or absence of the characteristic physical manifestations of abdominal aneurysm—a mass exhibiting an expansile pulsation, a palpable thrill, and an audible bruit—is again related to site and size. Of these, the former was most constantly present (75 per cent) in the syphilitic group.

10. Contrary to previous reports, the patients in this series with syphilitic abdominal aneurysms showed a high incidence of syphilitic involvement of the thoracic aorta and of the aortic leaflets—34 per cent had saccular thoracic aneurysms and an additional 18 per cent syphilitic aortic regurgitation.

11. The important roentgenologic findings are: (1) erosion of the vertebral column resulting from pressure of the aneurysm, the vertebrae commonly involved being the eleventh dorsal through the second lumbar, and (2) the presence of calcium deposits in the wall of the aneurysmal mass.

12. The prognosis of syphilitic abdominal aneurysm, though usually grave, may be quite variable. Although 70 per cent succumbed within 36 months after onset of symptoms, 17 per cent survived more than 5 years.

13. The case history of one patient who has survived for 28 years is reported.

Epstein [123] reviews most of the literature pertaining to abdominal aneurysms and adds 9 additional cases.

Lazarus and Marks [124] discuss abdominal aortic aneurysm in its relationship to urologic manifestations and record a case of this type presenting urinary symptoms. The possible effects of an upper abdominal aortic aneurysm on the kidneys may be due to changes in the local circulation, direct pressure on the kidney itself or interference with renal drainage. Should the aneurysm be situated above the origin of the renal arteries, one or both will eventually suffer from reduced flow of blood. However, a lesion situated below the origin of the renal arteries may eventually lead to dilatation of these arteries with resultant hyperemia of the kidneys, with the presence of occult blood in the urine. The pain of abdominal aortic aneurysm often simulates renal colic. The most frequent roentgenologic observations are of renal or ureteral displacement and osseous erosion. Lateral roentgenograms are of invaluable aid in demonstrating these conditions, and roentgenograms should be carefully searched for calcareous shadows adjacent to the renal silhouette.

The same authors [125] review the literature and report a case of aneurysm of the renal artery. In only 3 of 75 reported cases was syphilis mentioned as an etiologic factor. A history of trauma was elicited in 34.7 per cent of the reported cases. Other etiologic factors were atherosclerosis and systemic debilitating infections. Small aneurysms of the renal artery usually give rise to no symptoms. Larger aneurysms, however, usually produce symptoms the most common of which is pain in the loin (62.7 per cent). A mass was felt in the loin in 30 per cent of the recorded cases. The presence of an opaque ring shadow with dense periphery on the roentgenogram in the region of the renal pelvis is a valuable diagnostic sign. The indicated procedure in the treatment of aneurysm of the renal artery is immediate nephrectomy with ligation of the renal artery proximal to the point of origin of the aneurysm.

NEUROSYPHILIS

Incidence.—Of 218,133 selectees passing through the Armed Forces Induction Station, New York city, Guidotti and his co-workers [126] found

123. Epstein, J.: Aneurysms of the Abdominal Aorta, Ann. Int. Med. **22**:252 (Feb.) 1945.

124. Lazarus, J. A., and Marks, M. S.: Aneurysm of the Abdominal Aorta Associated with Urinary Symptoms, J. Urol. **52**:115 (Aug.) 1944.

125. Lazarus, J. A., and Marks, M. S.: Aneurysm of the Renal Artery—True and False—with Special Reference to Preoperative Diagnosis, J. Urol. **52**:199 (Sept.) 1944.

5.587 to have syphilis, the prevalence by race being 1.03 per cent for white persons and 12.16 per cent for Negroes. This study is particularly concerned with the results of examinations of the spinal fluid of 3,000 of the syphilitic selectees. "Sufficient pathologic changes to cause rejection" were found in 294 (9.5 per cent), all but 15 of whom had positive reactions to Wassermann tests of the spinal fluid.

Data on 1,176 blind persons receiving aid for the blind in Massachusetts have been coded in accordance with the standard classification developed by the Committee on Statistics of the Blind. Riemer [127] presents these data in tabular form, classifying the cases according to topography and type of disease, etiology and age at onset of blindness. In 128 cases (about 11 per cent of the whole number) blindness was due to syphilis, and in 101 of these it was due to syphilis acquired after birth. Twelve per cent of all blindness was due to atrophy of the optic nerve, and only 1.3 per cent to interstitial keratitis.

Syphilis of the Spinal Cord.—Adams and Merritt [128] present a valuable discussion of syphilis of the spinal cord. They describe the anatomic and physiologic considerations of the several forms of the disease, which they classify in four groups: (*a*) syphilitic meningomyelitis, which includes amyotrophic meningomyelitis, syphilitic spastic paraplegia, amyotrophic syphilitic myelitis and systematized spinal sclerosis; (*b*) spinal vascular syphilis; (*c*) syphilitic spinal pachymeningitis, including gumma of the spinal cord and syphilitic hypertrophic pachymeningitis, and (*d*) syphilitic poliomyelitis. Cases typical of the various clinical entities are briefly presented.

Tabes Dorsalis.—In a previous review,[1ᴿ] attention has been, called to the similarity between the lesions of tabes dorsalis and those produced experimentally in pigs on vitamin-deficient diets.

Follis and Wintrobe [129] report from their laboratory further experiments on swine in which deficiencies in vitamins of the B complex have been produced. Of particular interest have been the studies on the relationship of vitamin deficiency to the integrity of nervous tissues. It was first shown that degeneration of the peripheral nerves, dorsal root

126. Guidotti, F. P.; Carrier, R. N., and Stumpf, W. E.: Spinal Fluid Findings in Cases of Syphilis in the General Population of Males Between the Ages of Eighteen and Thirty-Eight Years Without Detectable Neurologic Changes, New York State J. Med. **44:**2488 (Nov. 15) 1944.

127. Riemer, H. B. C.: Topographic and Etiologic Study of 1,176 Indigent Blind Persons in Massachusetts: A Basis for Prevention of Blindness, Arch. Ophth. **32:**304 (Oct.) 1944.

128. Adams, R. D., and Merritt, H. H.: Meningeal and Vascular Syphilis of the Spinal Cord, Medicine **23:**181 (May) 1944.

129. Follis, R. H., Jr., and Wintrobe, M. M.: A Comparison of the Effects of Pyridoxine and Pantothenic Acid Deficiencies on the Nervous Tissues of Swine, J. Exper. Med. **81:**539 (June 1) 1945.

ganglion cells and posterior columns of the spinal cord should be pro-
duced when young swine were fed a basal diet (crude casein, sugar,
lard, salts and cod liver oil) supplemented only with crystalline
thiamine hydrochloride and riboflavin. Although the inclusion of nico-
tinic acid in this diet led to some improvement in growth of the animals,
changes in the nerves, ganglion cells, and spinal cord continued to
appear. When other vitamins of the B group became available, it was
shown that good growth could be obtained and neural lesions could be
prevented if choline, pyridoxine and pantothenic acid were added to the
basal diet already supplemented with thiamine, riboflavin and nico-
tinic acid. Finally, it was established that lesions could be produced in
sensory neurons when pyridoxine and/or pantothenic acid was excluded
from the diet.

The experiments here reported were undertaken to compare the
effects of a deficiency of pyridoxine and pantothenic acid on the nervous
tissues of swine. The demonstration that these vitamins may have spe-
cific actions on sensory neurons has obvious implications for some of
the fundamental problems of neurophysiology and neuropathology.
Follis and Wintrobe say:

> Observations were made on 2 separate groups, totalling 45 swine of both sexes.
> One group (series I) was placed on the deficient diet at about 32 days of age,
> the other (series II) at about 20 days of age. . . .
> When the pigs were received in the laboratory they were placed on the basal
> diet: Sheffield "new process" casein, 26.1 per cent; sucrose, 57.7 per cent; lard,
> 11 per cent; salt mixture, 5.2 per cent, and Mead's blended oil. Brewers' yeast
> was given until the experimental deficiency was begun, at which time crystalline
> vitamins were administered daily in the following amounts per kilo: thiamin
> hydrochloride, 0.52 mg.; riboflavin, 0.13 mg.; nicotinic acid, 1.20 mg.; choline
> chloride, 10.0 mg.; inositol, 0.1 mg. (series II) and para-aminobenzoic acid, 0.1 mg.
> (series II). Varying amounts of pyridoxine and/or calcium pantothenate were
> administered.

As the pigs died or were killed autopsies were performed as promptly
as possible.

> These experiments confirm previous studies from this laboratory and show that
> diets containing inadequate amounts of pyridoxine or pantothenic acid or both
> lead to degeneration of the sensory neurons of swine. A different morphological
> pattern has been observed in the two groups, however, especially when the patho-
> genesis of the lesions was studied during the early stages. Myelin degeneration
> of the peripheral portion of the sensory nerve appeared to be the initial change in
> pyridoxine-deficient animals. Axis cylinder degeneration almost immediately
> became apparent as well. Chromatolysis of the dorsal root ganglion cells was
> extremely inconspicuous, either early or late in the course of the deficiency.
> Atrophy, followed by necrosis and neuronophagia, was observed without supervening
> chromatolytic phenomena. In contrast, the initial morphological change found in
> animals whose diet was deficient in pantothenic acid has been pronounced chroma-
> tolysis of the dorsal root ganglion cells. Atrophy of these cells was not prominent.
> Only later could evidence of myelin and axis cylinder degeneration be detected in

the peripheral nerves and dorsal roots where it was never as extensive as that observed in the pyridoxine-deficient pigs. The nervous tissues of animals deficient in both vitamins revealed changes similar to those found when pyridoxine or pantothenic acid deficiency was present alone. . . .

The morphological changes described in this report would seem to indicate that the primary site of injury to the neuron in pyridoxine-deficient animals is in its peripheral process (myelin sheath and axon). In contrast, the initial locus of damage in pantothenic acid—deficient animals would seem to be in the cell body itself. It must clearly be borne in mind that such a conclusion is based entirely on morphological data. However, the hypothesis is an intriguing one and helps explain the differences in the pathologic pictures. Moreover, it has a basis of fact if the pathogenesis of some common neurological disease is considered.

The "primary" diseases of the nervous system can be divided pathologically into two types: myelinoclastic and polioclastic. . . .

The course of the degeneration of the nerve fibers was not specifically studied in these experiments. However, since degeneration of the sensory nerve roots and dorsal columns was not seen in animals deficient in either vitamin unless well marked changes were found in the peripheral nerves, it would seem that the latter, especially in pyridoxine deficiency, are the most vulnerable. . . .

Attention must be called to the changes in the spinal ganglion cells in a few of the animals deficient in pantothenic acid. Such lesions were not found in pyridoxine-deficient swine. These changes may further indicate that pantothenic acid plays a more important rôle than pyridoxine in the metabolism of the perikaryon. . . .

. . . the gait of the two groups of animals differed. Whereas pyridoxine-deficient animals showed a swaying and twisting of the legs as an early sign, those deficient in pantothenic acid rarely showed this symptom, but would lift one leg suddenly off the ground as though it were painful. . . . The onset of ataxia and the development of pathological lesions were earlier in the animals deficient in pantothenic acid. There was little difference, however, between the late manifestations in the two groups of animals. . . .

In view of the common acceptance of thiamin as "the antineuritic vitamin" it would seem worthwhile to mention that we have failed to produce lesions of the nerves in swine deficient in this vitamin.

Emmett [130] classifies the tabetic bladder as a "pseudo-cord bladder." He states that although it is true that tabes dorsalis may play a role in vesical dysfunction and urine retention, this role is one of minor importance. The part played by tabes dorsalis is only one of reduction in sensation, due to sensory disturbances of the posterior roots of the spinal nerves and of the posterior columns of the spinal cord. This delays normal reflex stimuli from reaching the bladder and the normal desire of micturition from reaching the threshold of consciousness until the bladder is more distended than normally. The final result over a long period is a distended, weakened bladder that is unable to expel its contents completely through a moderately obstructed vesical neck. As nearly all patients who have this type of vesical dysfunction are more than

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130. Emmett, J. L.: Transurethral Resection in Treatment of True and Pseudo Cord Bladder, J. Urol. **53**:545 (April) 1945.

40 years of age, the incidence of some form of obstruction is high. In nearly all these cases transurethral resection of the vesical neck will permit the patients to empty their bladders completely. The author believes that syphilis of the central nervous system (including tabes dorsalis) is not the important etiologic factor in urinary retention that it previously was thought to be.

Treatment.—(a) General: Solomon and his associates [131] outline briefly, for the benefit of Army physicians, the latest present day suggestions for the treatment of neurosyphilis. Outlines of treatment are recommended for the various forms of neurosyphilis to secure "the maximum benefit of treatment which can be secured by hospitalization in a general hospital not to exceed 3 months."

(b) Charcot Joint: In an article concerned primarily with treatment of the tabetic arthropathies, Key [132] lays special stress on early diagnosis. He believes that in the initial stages of Charcot's disease the involved joint first passes through an acute or progressive stage during which the tissues of the joint tend to disintegrate rapidly and are especially vulnerable to even mild injury. This is followed by a stage during which the swelling tends to subside, the excess synovial fluid to be absorbed and the bones and ligaments to toughen. Key advises complete rest for the early Charcot joint, preferably with the patient in bed. After the initial period of rest in bed the patient is allowed to resume weight bearing with as much protection as can be provided. In the treatment of the late stages of Charcot's joints conservative treatment is preferred to operative procedures.

(c) Complications of Fever Therapy: Jaundice is mentioned as a rare complication of artificial fever, occurring only in cases in which there is definite circulatory collapse or dehydration or in which the level of the blood chlorides is low. Contrary to this usual experience, MacDonald [133] has encountered 48 cases of jaundice in 250 patients treated with fever for sulfonamide resistant gonorrhea. In the twelve hours preceding fever therapy, the patients were given 6 Gm. of sulfathiazole or sulfadiazine. Treatment consisted of the maintenance of a temperature above 106 F. for seven hours. Clinical icterus was usually detected on the second or third day after fever. Five patients had extreme, 6 moderate and the remaining 37 mild icterus. Only 2 patients were

131. Solomon, H. C.; Moore, J. E.; O'Leary, P. A.; Stokes, J. H., and Thomas, E. W.: The Treatment of Neurosyphilis, Bull. U. S. Army M. Dept., November 1944, no. 82, p. 66.

132. Key, J. A.: The Treatment of Tabetic Arthropathies, Urol. & Cutan. Rev. **49**:161 (March) 1945.

133. MacDonald, R. M.: Toxic Hepatitis in Fever Therapy, Canad. M. A. J. **51**:445 (Nov.) 1944.

critically ill, and there were no fatalities. The author suggests that the high incidence of icterus in the present series may result from the effect of fever on a body with a relatively high blood level of sulfonamide drug. The possibility of infectious hepatitis does not seem to have been excluded.

Fredricks and Hoffbauer [134] have evaluated hepatic function in 31 neurosyphilitic patients given therapeutic benign tertian malaria. The criterion for a complete course of malaria was considered to be either forty hours of fever at or over 103 F. or one hundred and fifty hours of fever with the oral temperature at or over 100 F. The 31 patients included in the investigation were divided into two groups. The first 20 were given general diets. Because of the consistent hepatic disturbance observed, the use of liver-sparing diets (high carbohydrate, high protein and low fat) was added to the study. The last 11 patients were given alternately the special and the general hospital diet.

The hepatic disturbance resulting was evaluated by (1) the quantitative serum bilirubin test, (2) the cephalin-cholesterol flocculation test, (3) the amount of urobilinogen in a twenty-four hour sample of the urine and the two hour quantitative Ehrlich reaction of the urine and (4) the sulfobromophthalein sodium dye retention test. Quantitative serum bilirubin determinations were performed on all 31 patients. Twenty-four of the 29 patients studied adequately showed an increase in total bilirubin during the malarial fever. Elevations to 1.7 mg. or more of prompt direct reacting bilirubin per hundred cubic centimeters were considered significant and were observed in 8 cases. Six of the patients were receiving the "general diet," and 2 the special diet. Eighteen "general diet" patients and 6 "special diet" patients showed significant and comparable increases in their reactions to the cephalin flocculation test. Of 13 "general diet" patients significant increases of urobilinogen in the urine were noted in 9. The remaining 4 were not tested prior to malarial therapy, but 3 showed excessive excretion of urobilinogen in the course of their treatment. Eleven patients, 5 of whom were "general diet" and 6 "special diet" patients, were tested by the two hour Ehrlich method. Nine of the 11 showed significant increase in excretion of urobilinogen. There was no appreciable difference between the general and special diet groups. Retention of sulfobromophthalein sodium was tested in 8 patients before as well as during and immediately after therapy. Five of the 8 showed significant increases. However, in 3 patients retention of dye decreased in the course of their therapy. Again there was no appreciable difference between the general and special diet groups.

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134. Fredricks, M. G., and Hoffbauer, F. W.: A Study of Hepatic Function in Therapeutic Malaria, J. A. M. A. **128**:495 (June 16) 1945.

Fredricks and Hoffbauer say that more attention should be given to the use of liver-protective diets in therapeutic malaria. They feel that malarial therapy is contraindicated in the presence of clinically manifest hepatic disease (as, for example, cirrhosis). The use of tests of hepatic function before fever malarial therapy is advised.

Careful studies on the blood-clotting mechanism during the course of therapeutic malaria for neurosyphilis are reported by Diggs.[135] The platelet count, bleeding time, coagulation time, clot retraction time, extracorpuscular volume, capillary fragility and prothrombin concentrations were determined at weekly intervals for 40 white patients receiving Plasmodium vivax malaria, for 9 white patients with Plasmodium malariae malaria, and for 10 Negroes with Plasmodium falciparum malaria. The noteworthy observation was that thrombopenia developed in all patients during the febrile period. Although the fall in blood platelets varied according to the method of determination, the decrease in platelet count was approximately one half to one third of the preinoculation values. Platelet counts made by means of the indirect method of MacKay were usually within the range of 150,000 to 300,000 per cubic millimeter during the febrile period. With the direct Rees-Ecker method and with the indirect moist brilliant cresyl blue method platelet counts were often less than 100,000 per cubic millimeter, and in some patients less than 25,000 per cubic millimeter. The platelet counts did not significantly change during individual paroxysms and soon after termination of malarial therapy returned to normal preinoculation values. This important observation may explain some of the hemorrhagic reactions (purpura, epistaxis and vaginal bleeding) sometimes encountered in the course of therapeutic malaria.

(d) Electric Shock Therapy: Since Feb. 4, 1943, 34 patients with dementia paralytica have been treated with electric shock by Petersen [136] at the Rochester (N. Y.) State Hospital. Curare was used in conjunction with the treatment in 18 cases. Thirty of the patients were men and 4 were women. The ages ranged from 28 to 60 years. The number of shocks administered to a patient varied from two to thirty-seven. A total of five hundred and thirty-eight treatments were given to the entire group. The current used in the initial treatment in each case was 500 milliamperes applied for 0.2 second. If a convulsion was not induced, the current was increased by steps up to 650 milliamperes,

135. Diggs, L. W.: Platelet Count, Bleeding Time, Clotting Time, Capillary Fragility, Prothrombin Concentration and Clot Retraction in Paretics Receiving Therapeutic Malaria, Am. J. Clin. Path. **14**:534 (Oct.) 1944.

136. Petersen, M. D.: Electric Shock in the Treatment of Dementia Paralytica, Proc. Staff Meet., Mayo Clin. **20**:107 (April 4) 1945.

which is near the maximal output of the apparatus. If a seizure was not induced by this current, the time of application was lengthened.

Of the 34 patients treated, 20 showed great, 9 slight and 5 no improvements. Four of those showing slight improvement had a relapse, but there was improvement again after a second series of electric shock. Thirteen of the patients had previously received fever therapy, and 21 had not. Since there was considerable difference in the two groups and the number is small, no valid conclusions can be drawn from statistical comparison. The best response was obtained in the agitated group. Improvement in the cerebrospinal fluid was noted in the majority of 16 patients who had not previously been treated with fever therapy.

(c) Lumbar Puncture Headaches: Levin[137] has analyzed, from the standpoint of headaches, the results of lumbar punctures performed during a five and one-half month period on 2,217 syphilitic candidates for induction into the armed forces. The fluids were collected rapidly; the patients got on their feet immediately and were instructed to keep active and not to lie down. Only 15 cases of postpuncture headache severe enough to require rest in bed were reported. The patients responded to from one to three days of rest in bed and liquid diet. The rapid collection of spinal fluid and the maintenance of the erect position following puncture apparently decreased the number of postspinal headaches to less than 1 per cent. This is believed to be due to the more nearly normal intracranial pressure maintained by the erect position, preventing oversecretion and compensatory intracranial hypertension with resultant headache.

SYPHILIS AND PREGNANCY

Incidence in Australia.—Hughes's[138] study, based on the routine Wassermann and Kahn tests performed on 28,924 pregnant women, demonstrated that 160 (0.55 per cent) had a positive serologic reaction for syphilis. As this is the largest series yet published in Australia, it is a fair indication of the incidence of syphilis in pregnant women attending hospital antepartum clinics in that country.

Treatment.—The treatment of the antepartum patient with early infectious syphilis has always been a problem. The patient frequently presents herself for the first time so late in pregnancy that it is difficult to give her sufficient treatment. At Bellevue Hospital Speiser and his

137. Levin, M. J.: Lumbar Puncture Headaches, Bull. U. S. Army M. Dept., November 1944, no. 82, p. 107.

138. Hughes, T. D.: Syphilis in Pregnant Women: A Study Based on the Routine Wassermann and Kahn Tests Performed on 28,924 Patients, M. J. Australia **2**:273 (Sept. 9) 1944.

co-workers [139] adopted massive arsenotherapy for patients with early infectious syphilis and decided to give the same type of treatment to antepartum patients with early syphilis. Thirty-six pregnant patients with early infectious syphilis were treated. In this group the syphilitic lesions appeared in 16 during the first trimester, in 13 during the second and in 7 during the last trimester of pregnancy. In addition, 5 patients with early latent syphilis and 2 with late latent syphilis were treated.

Of the 43 pregnant patients treated, 6 received oxophenarsine hydrochloride alone; 1 patient received 1.2 Gm. of oxophenarsine hydrochloride in six days; 1, 0.88 Gm. in nine days; 3, 0.84 Gm. in six days, and 1, 0.72 Gm. in six days, depending on the dosage in vogue at the time. Eight patients received from 0.6 to 0.8 Gm. of oxophenarsine hydrochloride and two to three (typhoid vaccine) bouts of fever in seven to eight days. Twenty-nine patients were placed on the ten day plan of treatment finally adopted, with 0.5 to 0.6 Gm. of oxophenarsine hydrochloride and three to four bouts of fever in the ten day period. Twenty-three of these patients also received bismuth.

In the fever-treated group, vomiting frequently followed the first few injections of exophenarsine hydrochloride. In only 1 instance did a patient continue vomiting through the entire course of oxophenarsine therapy. One patient had erythema on the ninth day. In 3 patients epistaxis was encountered. There were no instances of jaundice, granulocytopenia or peripheral neuritis. Unfortunately, in the last patient treated arsenical encephalopathy developed, and the patient died after the fifth injection of 0.07 Gm. of oxophenarsine hydrochloride with one previous episode of fever.

Combining the results of the three plans of therapy, of the 30 babies delivered 23 have seronegative reactions, 14 having been followed one to twenty-four months. For results 7 have been classified as failures. The probable good results (23 out of 30) would then be at least 76.6 per cent.

In the routine treatment of syphilis in pregnancy, a direct relationship can be observed in the results obtained and the time in pregnancy at which treatment was started. No such relationship is apparent in the cases of intensively treated patients. Of the 9 mothers who were treated in the first trimester of pregnancy, 7 had babies classified as giving a good response to the treatment, and of the 13 who were treated in the second trimester, 9 delivered babies free from syphilis. Eight mothers were treated in the third trimester, and 7 of their babies were healthy.

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139. Speiser, M. D.; Wexler, G.; Thomas, E. W., and Asher, H. A.: The Rapid Treatment of Early Syphilis During Pregnancy, Am. J. Obst. & Gynec. **49**:214 (Feb.) 1945.

Most authorities have felt that all pregnant women who have or have had syphilis should be treated with each pregnancy, irrespective of previous therapy or the status of their serologic tests. After a nonpregnant patient finished the rapid treatment, no further therapy was given unless a relapse occurred. Thirty-two of the intensively treated patients subsequently became pregnant and received no further treatment. Two had previously been treated for early latent syphilis and 30 for secondary syphilis. Of these 32 patients, 27 delivered healthy babies, 26 at term and 1 after thirty weeks of gestation. Five had spontaneous abortions, of which only 1 was due to syphilis. Of the 27 who had healthy babies, 4 delivered ten to eleven months after antisyphilitic treatment; 8 delivered twelve to seventeen months; 5 delivered eighteen to twenty-three months, and 10 delivered twenty-four months after their intensive therapy. Twenty-five mothers had negative intrapartum serologic reactions for syphilis. All of these had seronegative babies. Two mothers had positive intrapartum serologic reactions for syphilis; 1 baby was seronegative at birth, and 1 was seropositive but became seronegative within one month.

Among the 487 patients with early syphilis treated by Neilson and his co-workers [47] there were 20 pregnant women. These patients received by intravenous drip 900 to 1200 mg. of oxophenarsine hydrochloride over a period of five days. Seventeen of these women were followed until delivery. One miscarriage occurred at three months. Fourteen babies born at term were normal "in appearance," and 2 babies (11.8 per cent) were definitely syphilitic. Two of the 14 normal-appearing babies had positive reactions to Kahn tests but were not yet 3 months of age. The authors point out that the follow-up of treated patients has not yet been long enough for a proper evaluation of intensive chemotherapy.

CONGENITAL SYPHILIS

Incidence.—Kalz [140] attempted to determine the responsibility for the occurrence of congenital syphilis. Is the high incidence of the disease due to ignorance on the part of the mother, to oversight on the part of the physician or to both? The mothers of 74 congenitally syphilitic children in the author's service in Montreal were questioned regarding their antepartum care. In some instances more detailed information was obtained from the physician by whom the patient had been seen. In 17 instances no physician had been consulted during pregnancy, and in 1 instance treatment had been refused. Ignorance of the mothers, therefore, accounted for the birth of 18 syphilitic children. In the remaining 56 cases responsibility rested with the physician. In

140. Kalz, F.: Congenital Syphilis, Canad. M. A. J. **52**:179 (Feb.) 1945.

49 cases no prenatal serologic tests for syphilis had been done; in 5 instances infection occurred in the course of pregnancy and was overlooked, and in 2 cases the physician ignored a report of a positive serologic reaction for syphilis. From this study, Kalz believes that emphasis should chiefly be placed on the education of physicians.

Teeth.—Bauer [141] reports a histologic study of the tooth buds and jaws of 4 fetuses and 2 infants with congenital syphilis. Spirochetes were demonstrated throughout the bony structure of the tooth and jaw but were particularly prevalent about and within the tooth buds, a site of intense growth activity. Tissue reaction in the form of plasma cells and fibrosis lagged behind the appearance of masses of spirochetes and did not reach a maximum until after birth. Evidence of any systemic disturbance of calcification, such as occurs in rickets, was lacking in the cases studied. The author believes that the chronic syphilitic inflammation of the tooth sac produces the enamel hypoplasia of the deciduous teeth and, by pressure on the early tooth bud, results in the characteristic distortion of the crown of the permanent teeth (Hutchinson incisor, mulberry molar).

Bone Lesions.—Russo and Shryock [112] analyzed the roentgenographic changes in the bones of 46 patients with congenital syphilis. Their ages ranged from newborn to 19 years. Twenty patients were older than 1 year; 6 were from 5 to 12 months of age, and 20 were less than 5 months of age. The serologic test of the blood for syphilis elicited positive reactions in 43 of the 46 patients. In the great majority of the patients there was roentgenographic evidence of a combination of osseous lesions. Periostitis could be detected in 42 patients, osteochondritis in 21, osteitis in 17 and osteomyelitis in 11. There were 5 pathologic fractures.

The most prevalent lesion in very young infants was osteochondritis with associated periostitis. In older children, osteitis and osteomyelitis, associated with lesions of other types, occurred in almost equal proportions. Diagnosis of syphilitic lesions of bone in older children on the basis of the roentgenologic evidence is more difficult than in young babies.

Interstitial Keratitis.—Bilateral interstitial keratitis occurs predominantly in patients with congenital syphilis. The association of

141. Bauer, W. H.: Tooth Buds and Jaws in Patients with Congenital Syphilis: Correlation Between Distribution of Treponema Pallidum and Tissue Reaction, Am. J. Path. **20**:297 (March) 1944.

142. Russo, P. E., and Shryock, L. F.: Bone Lesions of Congenital Syphilis in Infants and Adolescents: Report of Forty-Six Cases, Radiology **44**:477 (May) 1945.

deafness is not uncommon in this group of syphilitic patients. Cogan [143] reports 4 examples of interstitial keratitis associated with vertigo, tinnitus and deafness occurring in persons in whom there were no signs or symptoms of syphilis from the history, physical examination or serologic tests. In 3 patients the clinical observations were identical. All were young women whose presenting complaints were severe vertigo, tinnitus, progressive bilateral deafness, pain in both eyes, ciliary injection, photophobia and somewhat reduced vision. Examination showed nerve deafness with absence of labyrinthine function, a deep keratitis of both eyes characterized by patchy infiltration of the deep corneal stroma, little reaction in the anterior chamber and no apparent abnormalty of the iris. The onset of vestibuloauditory symptoms and of ocular symptoms occurred within a few weeks of each other. The course of the illness was chronic, with progression of deafness, diminution of vertigo and unchanged ocular signs over a two to ten month period. The fourth patient was a man in whom the vestibuloauditory symptoms were relatively mild and the keratitis was unilateral and showed complete remission between attacks. which continued over a period of months. The signs, symptoms and course of the syndrome differ from those of the interstitial keratitis and nerve deafness of congenital syphilis. The etiologic agent is not apparent in the present cases.

Castroviejo [144] discusses keratectomy (the excision of external layers of the cornea) in the treatment of corneal opacities. A brief description is given of the different types of keratectomy utilized by the author. Superficial keratectomy in selected cases offers the ideal method of improving the visual acuity of the affected eye. Not all corneal opacities are suitable for corneal transplantation (keratoplasty). It is in these cases that keratectomy is apparently of principal value.

SYPHILIS ASSOCIATED WITH OTHER DISEASES

Tuberculosis.—The combination of syphilis and pulmonary tuberculosis continues to present difficult problems to the phthisiologist as well as to the syphilologist. Two of these problems, the effects of (*a*) syphilis and (*b*) antisyphilitic treatment on the course of pulmonary tuberculosis in the Negro, are considered by Hoffman and Adams [145] in an analysis of 1,705 adult patients admitted consecutively to a tuberculosis sanatorium. The prevalence of syphilitic infection in this

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143. Cogan, D. G.: Syndrome of Nonsyphilitic Interstitial Keratitis and Vestibuloauditory Symptoms, Arch. Ophth. **33**:144 (Feb.) 1945.

144. Castroviejo, R.: Keratectomies for Treatment of Corneal Opacities, Arch. Ophth. **32**:11 (July) 1944.

145. Hoffman, R., and Adams, G. G.: Syphilis and Pulmonary Tuberculosis in the Negro, Am. Rev. Tuberc. **50**:85 (Aug.) 1944.

group as determined by serologic tests was 29.7 per cent, of which 10 per cent was early latent syphilis, 70 per cent late latent syphilis, 15 per cent syphilis of the central nervous system and 5 per cent cardiovascular syphilis.   Analysis of the data presented revealed no significant difference between the syphilitic and the nonsyphilitic groups in the amount of pulmonary disease, the predominant type of tuberculous lesion or the percentage of deaths.   Of the patients with minimal tuberculosis, 24.7 per cent had syphilis; of those with moderately advanced disease, 29.2 and of those with far advanced disease 31.1 per cent.   Since most studies of this nature indicate that the percentage of syphilis is highest in the group with far advanced tuberculosis and lowest in those with minimal involvement, the inference is usually drawn that the presence of syphilis unfavorably affects the patient's resistance to tuberculosis.   The authors, taking issue with this viewpoint, suggest that the economic status of the patient is the important consideration.

In respect to the administration of antisyphilitic treatment to tuberculous patients, the authors have a rational approach.   Patients with early infectious syphilis and those who are syphilitic and pregnant are treated regardless of the status of their tuberculosis.   Antisyphilitic treatment is also administered to those with early latent or late cardiovascular syphilis or neurosyphilis and to those patients, who on admission, "need one or two courses to complete treatment." Patients with late latent syphilis are treated only when the prognosis from the standpoint of tuberculosis is good.   The authors are not convinced that the arsenicals exert any deleterious effect on the course of pulmonary tuberculosis.   They have observed only a single instance in which they were able to ascribe a flare-up of tuberculosis to the administration of an arsenical drug.

Diabetes Mellitus.—The causal status of syphilis in the etiology of diabetes mellitus has long been a controversial subject.   Other than in infants with early congenital syphilis, pancreatic lesions which could be ascribed to syphilitic infection have been found only by Warthin, whose studies have never been confirmed.   The recent clinical reports of Joslin and of Williams [1g] failed to indicate any beneficial effect of antisyphilitic treatment on the course of diabetes mellitus in patients with syphilis.

In a long-term clinical study (follow-up periods of ten to fifteen years), Perkin [146] records observations on 54 syphilitic patients in a total of 550 diabetic patients.   The diagnosis of syphilis for these patients was made on the basis of positive serologic reactions for

146. Perkin, F. S.: Syphilis and Diabetes Mellitus: A Long-Term Clinical Study, Ann. Int. Med. **21**:272 (Aug.) 1944.

syphilis in 42, and for 12, with negative serologic reactions, on anamnestic data. The author implies that all patients had late syphilis, the majority of them latent, since late manifestations were found in only 7 (neuro-syphilis in 5, benign late and cardiovascular in 1 each) though admittedly few examinations of spinal fluid were performed. In this small series, diabetic patients with syphilis were somewhat older than patients in the nonsyphilitic group and had an unusually mild form of diabetes.

In attempting to evaluate the effect of antisyphilitic therapy on the course of diabetes, 19 patients were studied, 14 of whom in Perkin's opinion showed varying degrees of improvement in tolerance following antisyphilitic treatment; 5 showed no improvement. It is not clear from the report how well other factors were controlled which might influence the course of diabetes. The author states, "In some cases, when feasible, no diabetic treatment, as diet or insulin, was prescribed."

Gonorrhea.—Guthrie [147] studied the prevalence and incidence of syphilis among 396 persons who had gonorrhea or had been exposed to it admitted to the Venereal Disease Division of the Johns Hopkins Hospital from Aug. 1, 1942, through May 30, 1943. Persons found to have gonorrhea during routine examination of patients with primary or secondary syphilis were excluded. The author summarizes his observations as follows:

Thirty-one per cent of gonorrhea patients and 39 per cent of contacts had or had had syphilis on admission. These percentages are not significantly different. Negroes had syphilis three times as frequently as whites; female patients more often than male patients. The age specific syphilis rates in Negroes rose from about 5 per cent in the group under 10 years of age to 50 per cent in the 30-to 39-year group.

One hundred and twenty-eight nonsyphilitic gonorrhea patients were re-examined for syphilis during the twelve weeks following admission. They accumulated 840 person-weeks of observation, and three were observed to have developed syphilis. This relatively low rate at which gonorrhea patients develop syphilis does not justify frequent blood testing. Patients may be inspected for lesions when the necessary observations for gonorrhea are made. Serologic tests for syphilis should be made on admission and at four-or six-week intervals during the next twelve [preferably sixteen, since the advent of penicillin] weeks.

Cameron and Chapman [148] present a study which should shock even the most torpid health department into a soul-searching inquiry as to

147. Guthrie, N. W.: Syphilis in Gonorrhea Patients and Contacts, Am. J. Syph., Gonor. & Ven. Dis. **28**:583 (Sept.) 1944.

148. Cameron, A. R., and Chapman, A. L.: Prevalence of Gonorrhea Among Syphilitic Patients: A Study Made in Delaware in 1943, Ven. Dis. Inform. **25**: 238 (Aug.) 1944.

its present methods of diagnosing and treating gonorrhea. A random survey was made of 412 male syphilitic patients attending venereal disease clinics sponsored by the Delaware Board of Health. Ninety-six per cent were Negroes. No patient was interviewed or examined more than once, and cultures were not available. The reported prevalence of gonorrhea is therefore, in all probability, far below the actual prevalence. Eighty-two (20 per cent) of the 412 patients had a urethral discharge which was positive on spread for gram-negative intracellular diplococci. Fifty additional patients had a urethral discharge reported (on the basis of 1 spread) as nonspecific. Eighty-nine per cent of the patients admitted having had a urethral discharge in the past. This study suggests that the present methods of dealing with gonorrhea are ineffective from the standpoint of diagnosis, treatment and epidemiology.

YAWS

Bones and Joints.—Helfet[149] states that yaws is the commonest disease of bones and joints in the tropics. Whereas syphilis tends to attack the bones and joints slowly and relatively silently, yaws present a more rapid and painful picture in many instances. Symptoms are usually of only a few weeks' duration, during which time striking roentgenographic changes develop. In yaws, a juxta-articular lesion may simulate arthritis of the joint itself, with pain, tenderness, swelling. muscle spasm and limitation of movement. When the shaft of a long bone is involved, a picture resembling septic osteomyelitis may result. The onset of symptoms often follows trauma and may be heralded by fever. The tibia, the lower end of the femur, the inner end of the clavicle and the lower end of the humerus appear to be the sites of election. Roentgenographic examination may show increase in diameter of the bone, considerable increase in density and single or multiple punched-out areas. More frequently, however, in this rapidly progressing type of yaws there is subperiosteal necrosis of the cortex, with raising of the periosteum, and the deposition of periosteal new bone, which in some cases is so dense as to simulate osteogenic sarcoma or the "onion-layering" of a Ewing tumor. Pathologically, the lesions consist of edematous, almost myxomatous-appearing tissue. A microscopic section shows infiltration of small round cells, many plasma cells and perivascular cuffing, but little or no endarteritis obliterans, which is characteristic of syphilis. Yaws tends to attack joints and tendon sheaths as well as bones. It is common to find a patient with ganglions involving the dorsal tendons of wrists or feet.

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149. Helfet, A. J.: Acute Manifestations of Yaws of Bone and Joint, J. Bone & Joint Surg. **26**:672 (Oct.) 1944.

In joints the disease is relatively painless, and the joint cartilage is not involved. When treatment with an arsenical drug is administered the response is dramatic. Subjective symptoms subside in one or two weeks, but the actual tumors subside much more slowly. Roentgenographic evidence of consolidation of the lesion can be demonstrated within six weeks.

Juxta-articular nodules have been .described in association with syphilis, with the arthritides and with several tropical diseases, notably yaws, filariasis and nocardiosis (a fungous infection). Chambers [150] reports the presence of these nodules in 128 patients observed in rural Jamaica, where yaws is endemic. Of these, 110 gave a history of yaws; only 21 of the 128 patients had received any previous treatment. He points out that the incidence of juxta-articular nodules is highest in yaws-endemic areas farthest removed from centers for treatment (about 1 per cent of the total number of infected persons) and lowest in areas with nearby facilities for treatment. Multiple nodules are the rule, the common sites being elbow and knee joints. The lesions respond slowly to antiyaws treatment, but in the author's experience bismuth subsalicylate was as effective as neoarsphenamine.

Penicillin Treatment of Yaws.—Whitehill and Austrian [151] have treated 17 patients with primary or secondary yaws, in all of whom Treponema pertenue was demonstrated on dark field examination before treatment. About 500,000 units of penicillin was administered intramuscularly in doses of 15,000 units, every four hours day and night for five to six days. All of the patients were Fijians. Although 6 of the patients had received previous arsenical or bismuth treatment ·in each case, the lesions were progressive before the start of penicillin therapy. Patients were hospitalized throughout the period of observation. Spirochetes disappeared from the cutaneous lesions of all but 1 patient within fifteen hours, and in the single exception within forty hours. With one exception all cutaneous manifestations of yaws were completely healed within three weeks after the start of treatment. Serologic reactions were positive in all patients and did not respond over the short period of observation. In an addendum Whitehill and Austrian submit similar results for an additional 25 patients, and a single case of tertiary yaws is reported in detail. In this case the patient had numerous areas of destruction and periosteal proliferation in a number of bones. The patient had been refractory to other therapy

150. Chambers, H. D.: Juxta-Articular Nodules, Arch. Dermat. & Syph. **50:** 105 (Aug.) 1944.

151. Whitehill, R., and Austrian, R.: Treatment of Yaws with Penicillin, Bull. U. S. Army M. Dept., March 1945, no. 86, p. 84.

and was therefore given a total of 1,000,000 units of penicillin in about eleven days. The lesions healed slowly, and therefore after an unstated interval following the first course of treatment the patient received an additional 2,400,000 units of penicillin. Subsequently all cutaneous lesions healed completely, and roentgenologic examination showed bony repair.

Lofgren [152] has also reported the favorable result of treatment with penicillin of a single patient with yaws.

152. Lofgren, R. C.: Yaws Treated with Penicillin: Report of a Case, U. S. Nav. M. Bull. **43**:1025 (Nov.) 1944.

Correspondence

ARACHNODACTYLY (SPIDER FINGERS)

To the Editor:—Apparently H. Gray's article on "Arachnodactyly (Spider Fingers)" in the April issue of ARCHIVES OF INTERNAL MEDICINE (**75**:215, 1945) can easily be interpreted as a calling to task of the specialties, specifically of ophthalmology. As an ophthalmologist, I should like to attempt some small defense in an endeavor to disintegrate any unwritten misconceptions concerning the specialist's being weaned away from Mother medicine. Unwittingly, this article, appearing in a journal of internal medicine, shows just this shortcoming, for the author has overemphasized linear measurements at the expense of medicine, surgery, orthopedics, genetics and ophthalmology, and has attempted to replace the investigator's eyes with dimensional analyses.

In order to support these allegations it is necessary to elaborate on some, but by no means all, of the discrepancies which appear in the article, for they might be digested with facility and assimilated as readily unless they become irrigated first with the well known saline solution.

For example: The author mentions feeblemindedness as one of the characteristics of the syndrome, the statement being made rather innocuously. Nevertheless, in a review of 204 cases, Rados (ARCH. OPHTH. **27**:477 [March] 1942) stated, "As a rule, the nervous system escapes implication. The general intelligence often is particularly good." In the 204 cases reviewed by this same author an occasional patient was shown to have some mental retardation but not any degree of feeblemindedness. An outstanding characteristic of these cases is the senile, sad, aged and melancholy facial expression, which for some unknown reason has been confused with the patient's mentality. The case reports certainly do not show any reason for inserting feeblemindedness in the syndromic triad.

In another paragraph Dr. Gray states: "In some of the reports of cases the diagnoses were not warranted by the measurements given; in many of the cases the measurements were fragmentary, perhaps only of one finger or of one phalanx, and, finally, in most cases the landmarks used were so obscure as to prevent comparisons by the reader."

Should it be pointed out that the diagnosis is not determined by any measurements? The syndrome is strikingly apparent and requires only a vague recollective knowledge of its cardinal signs to be recognized. It is true that most of the cases reported in the literature are either of the clearcut, typical variety (typus Marfan) or of the forme frustre grouping. The latter class of necessity has questionable dimensions. As implied by the terminology, such a classification indicates that this is to be anticipated, since these cases are incomplete genetic problems which we have not as yet satisfactorily explained. Measurements in such a group could not conform to any fixed pattern. There are cases reported in which there is symmetric bilateral lenticular subluxation with certain skeletal defects associated with melancholic expression in the absence of arachnodactyly.

Measurements according to Gray's standards and their interpretations would result in discarding these from the syndrome even as so-called forme frustre cases. This in turn would lead to a lack of understanding of the underlying cause of the syndrome and would not aid in clarification of the present concept of the cause of Marfan's syndrome, namely, so-called genetic coupling. At present, it is believed

that a switching of certain elements in the genes of the chromosomes is the factor most likely to be responsible for the appearance of the atypical cases of Marfan's syndrome.

Besides the typical cases in which the syndrome is of complete development, there are incompletely developed cases in which the general habitus recalls the typical picture, although not all the cardinal symptoms of the syndrome are present. A symptom complex may be shown to be grouped around a central dominant characteristic which in the case of Marfan's syndrome is the marked slenderness or gracility of the extremities. There, different single symptoms grouped about the dominant characteristic are caused not by multipotential genes but by genes located close to one another within the same chromosome (Marfan, M. A.: Un cas de déformation congénitale des quatres membrés, plus pronouncée aux extrémités, characterisée par l'allongement des os, avec un certain degré d'amincissement, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220, 1896).

In still another paragraph the author maintains: "Similar statements are common about reported cases but should be regarded skeptically; more than once 4 instances in the same family have been reported . . . hence it is probable that a number of instances in the literature stated to be isolated could have been demonstrated to be really familial if measurements had been made of the immediate relatives."

Some of the greatest ophthalmologists, among whom must be included Weve, Irgersheimer, Fleischer, Hamburger, Vogt, Franceschetti, Sorsby, Amsler, Coppez, Buecklers, Passow and Viallefonte, must be guilty of failure to recognize the really familial nature of this disease because they did not measure the skeletal structure of the relatives. This indeed would be very strange, for among these ophthalmologists are included men who have contributed much in the field of genetics as well as in that of congenital ocular anomalies. These men, trained to see microscopic similarities and differences not only in the eye but also in the chromosome should be able to detect the familial likenesses of freaks such as those with the Marfan syndrome without having to conduct intricate anthropologic measurements, since the habitus of the Marfan syndrome causes the laymen to stop and look with mouth ajar.

The author in reporting case 1 stated that "his hands, feet and ears were noted at once as large, and the nurses called him 'infant Hercules.'" Since in 80 per cent of the cases the patients have subluxated lens and in 50 per cent they have a congenital cardiac condition—why not just check "Hercules" for these conditions?

At this point it might be worth while to mention that from the very first case report (that of Marfan previously cited) the hereditary character of the case was suspected. In the earliest cases reported there is evidence to show that the hereditary nature of the condition was suspected, for the case reports point out in detail "that a brother of one patient had a congenital cataract and that one of the patient's sisters had remarkably large hands as did a maternal grandfather."

In his summary the author states: "a new contribution to the knowledge concerning this anomaly was made through a careful study of physical build by means of anthropologic measurements."

In reviewing this original contribution the author has made, and after divorcing the mathematic and indicial "confusors," it appears that the following claims have been made: (a) "microcephaly—apparently a new finding in connection with arachnodactyly"; (b) an amazing disproportion between the upper and lower ends of the trunk; (c) "the length of the patient's hands as a whole . . . and the slenderness of the hand"; (d) slenderness of the foot. (e) "Arachnodactyly manifests a partial gigantism in the upper limb, which is not of like degree in the three

segments, but progressively more pronounced as one proceeds away from the body. For the lower extremity . . . the reverse is found."

As regards microcephaly as a new finding—this is true only of 1 case, namely, the author's. Other cases show a distinct tendency toward dolichocephaly, which is the usual thing, although an occasional case of brachycephaly has been reported.

The author states that an amazing disproportion between the upper and lower ends of the trunk exists, and the biacromial to bicristal ratio is so striking as to occur in less than 1 to 1,000 cases. Both these claims are new ones and should be looked for. They produce such striking pictures that they should be recognized readily without mensuration.

The other claims of the author have long ago been emphasized in the literature. The length and slenderness of both hands and feet and elongation of the upper extremity have been best expressed by stating that the patient's span exceeded his height and that the hands were extremely gracile. The reverse phenomenon for giantism in upper and lower limbs in the three segments has been described only in a single case.

From scrutiny of Gray's photographs certain features of importance in the syndrome may be gleaned which received no mention from the author. They include: (*a*) sparsity of subcutaneous fat; (*b*) bowing of elbows; (*c*) overlapping of toes, and (*d*) webbing of fingers.

In conclusion, I wish to refer the author and all readers interested in Marfan's syndrome to the excellent article written by Rados, a very careful review in which every one of the 204 cases reported up to that time is analyzed and, in addition, a very complete and satisfactory anthropologic tabulation appears. Furthermore, Rados' conclusion may be worthy of emphasis: "The arachnodactylic habitus is extremely obvious."

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Book Reviews

Rypins' Medical Licensure Examinations. Edited by W. L. Bierring, M.D. Fifth edition. Price, $6. Pp. xxii + 546. Philadelphia, London and Montreal: J. B. Lippincott Company, 1945.

President Lowell of Harvard once remarked that examinations, like most human beings, are imperfect and that their results are only approximate. Harold Rypins, like Mr. Lowell deeply tinged with Harvard crimson, apparently agreed with this philosophy, for in 1933 he wrote the first edition of this book.

The preface to the first edition still lives and must be studied to appreciate why a fifth edition ever proved necessary. Rypins believed that the average graduate of an American medical school is well prepared for the practice of his profession yet needs assistance in the use of the material with which his head has been filled by his professors in order to make of examinations a relatively pleasant undertaking to be faced without trepidation. Accordingly, he attempted to prepare a serious and orderly summary of such parts of the medical curriculum as are ordinarily considered important by various examining boards.

The success of the venture was notable. Until 1939 new editions were forthcoming at two year intervals. The fifth edition, under a new editor, has just appeared.

Rypins attempted to bring each edition up to date and to avoid unnecessary words. This plan has been adhered to, so that the latest edition, while modern, is not much larger than was the first. Rypins divided his book into twelve chapters —an arrangement which has been maintained. The new edition has acquired eight eminent collaborators, who have helped materially to strengthen the work.

The Journal of the American Medical Association (**101**:1100-1101 [Sept. 30] 1933) reviewed the first edition, and what was said of the book then is true today. It is a unique volume. Its text is clear and concise. It does not pretend to be a complete textbook or to teach anything new. Its only object is to assist any student in the intelligent and practical use of what he knows. It should be helpful for this purpose.

What to Do About Vitamins. By Roger J. Williams. Price, $1. Pp. 56. Norman, Okla.: University of Oklahoma Press, 1945.

This is a satisfactory little book to recommend to patients or other laymen interested in and wishing information about foods and nutrition. The author provides practical, easily understood directions on how to choose foods so that the taking of extra vitamins is unnecessary. Good diet planning demands more attention than many have supposed. It is necessary because of the prominent position in the food environment of refined fuel foods that fail to carry their share of the "lubricants" (vitamins and minerals) required for good health. The food producer, by raising the nutritional quality of his products, should play an important part in improving the diet of the public, and "the time should come when the housewife will not have to exercise as much caution as she does now, and when she can, by the simple expedient of diversifying her purchases, furnish her family with a completely adequate as well as attractive diet."

The author, Roger J. Williams, director of the Biochemical Institute of the University of Texas, is one of the leaders in the biochemical research which has contributed so greatly to the current knowledge of nutrition. He is best known for his discovery, in 1933, of pantothenic acid and, more recently, of folic acid.

EFFECTS OF PLASMA AND FLUID ON PULMONARY COMPLICATIONS IN BURNED PATIENTS

Study of the Effects in the Victims of the Cocoanut Grove Fire

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THE victims of the Cocoanut Grove disaster, which occurred in Boston on the night of Nov. 28, 1943, offered a rather unusual opportunity for the study of the types of injury to the respiratory tract which may be expected when persons are exposed to smoke and flame resulting from rapid and extensive combustion in a relatively confined space. Since air conditioning has become commonplace and is increasing in popularity, the circumstances which gave rise to the Cocoanut Grove disaster might easily be duplicated in civilian life in situations in which combustible materials or mixtures of gases start to burn and cause an early disruption of the ventilating systems. Similar situations may arise when fires are caused by inflammable liquids or when explosives are set off or when fires gain headway in the holds of ships—and probably under many other circumstances. Few reports on the combination of extensive surface burns and severe injuries of the respiratory tract similar to those of the persons hurt in the Cocoanut Grove fire are available in the literature.[1]

1. (a) Nichols, B. H.: The Clinical Effects of the Inhalation of Nitrogen Dioxide, Am. J. Roentgenol. **23**:516-520, 1930. (b) Beckey, K., and Schmitz, E.: Klinische und chemische Beiträge zur Pathologie der Verbrennung., Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:416-432, 1918-1919. (c) Fischer, B., and Goldschmid, E.: Ueber Veränderungen der Luftwege bei Kampfgasvergiftung und bei der Verbrennung, Frankfurt. Ztschr. f. Path. **23**:11-33, 1920.

One of the important features of the management at the Boston City Hospital of the patients who were injured in the Cocoanut Grove fire was the rather large volumes of plasma and other fluids that were used in the treatment of many of the patients. That, too, was considered to be rather unusual at the time, although it has since become a not infrequent practice in the treatment of patients with extensive surface burns. We are aware of no other reports of the use of similar amounts of plasma and other parenteral fluids in persons with such extensive pulmonary lesions. An analysis of the effects of this therapy on the complications in the respiratory tract in the present cases may, therefore, be of interest. Details of the clinical features of these complications, as observed at the Boston City Hospital, are recorded elsewhere,[2] and a description of the observations made concerning the victims of this fire who were treated at the Massachusetts General Hospital is included in the comprehensive report from that hospital.[3] The surgical and biochemical studies on the patients treated at the Boston City Hospital are considered in separate reports by Dr. C. C. Lund and Dr. F. H. L. Taylor and their associates.[4]

2. (*a*) Finland, M.; Davidson, C. S., and Levenson, S. M.: Clinical and Therapeutic Aspects of the Conflagration Injuries to the Respiratory Tract Sustained by Victims of the Cocoanut Grove Disaster, to be published. (*b*) Finland, M.; Ritvo, M.; Davidson, C. M., and Levenson, S. M.: Roentgenologic Findings in the Lungs of Victims of the Cocoanut Grove Disaster, Am. J. Roentgenol. **55**: 1-15, 1946.

3. Cope, O., and others: Symposium on the Management of the Cocoanut Grove Burns at the Massachusetts General Hospital, Ann. Surg. **117**:801-965, 1943.

4. (*a*) Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S.; Adams, M. A., and MacDonald, H.: Abnormal Nitrogen Metabolism in Burns; Science **97**:423 (May 7) 1943. (*b*) Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S., and Browder, N. C.; Problems of Protein Nutrition in Burned Patients, Ann. Surg. **118**:215-224 (Aug.) 1943. (*c*) Clowes, G. H. A., Jr.; Lund, C. C., and Levenson, S. M.: The Surface Treatment of Burns, ibid. **118**:761-779 (Nov.) 1943. (*d*) Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S., and Adams, M. A.: Abnormal Nitrogen Metabolism in Patients with Thermal Burns, New England J. Med. **229**:855-859 (Dec.) 1943. (*e*) Taylor, F. H. L.; Davidson, C. S., and Levenson, S. M.: The Problem of Nutrition in the Presence of Excessive Nitrogen Requirement in Seriously Ill Patients with Particular Reference to Thermal Burns, Connecticut M. J. **8**:141-147 (March) 1944. (*f*) MacDonald, A. H.; Levenson, S. M.; Davidson, C. S.; Tagnon, H. J., and Taylor, F. H. L.: Studies on the Peripheral Blood in Patients with Thermal Burns: I. Thrombocytopenia, Science **99**:519 (June 23) 1944. (*g*) Taylor, F. H. L.; Levenson, S. M., and Adams, M. A.: Abnormal Carbohydrate Metabolism in Human Thermal Burns, New England J. Med. **231**:437-445 (Sept. 28) 1944. (*h*) Levenson, S. M.; Davidson, C. S.; Lund, C. C., and Taylor, F. H. L.: The Nutrition of Patients with Thermal Burns, Surg., Gynec. & Obst. **80**:449-469 (May) 1945.

For convenience the severity of the injuries to the respiratory tract were graded according to the symptoms and physical findings roughly as follows:

Grade   Clinical Manifestations

0. No signs or symptoms referable to the respiratory tract.
1. Signs and symptoms, including mild laryngitis, limited to the upper respiratory passages.
2. Evidence of involvement of the trachea and bronchi, or abnormal signs in the lungs other than those of frank consolidation.
3. Dyspnea, cyanosis, wheezing or transient stridor, or frank signs of consolidation.
4. Evidence of extensive pulmonary involvement or of obstruction to the airways necessitating tracheotomy or resulting in severe asphyxia.

In general, the extent of the abnormalities found in the lungs by roentgenologic examination reflected the severity of the clinical findings fairly closely, but in an appreciable number of cases the clinical symptoms were much more severe than might have been expected from the lesions visible in the roentgenograms.[2b] There was also some direct correlation in most cases between the extent of the surface burns and the severity of the injuries to the respiratory tract. Both here and at the Massachusetts General Hospital, however, there were cases of severe and even fatal respiratory lesions in which surface burns were either absent or minimal. Likewise, at both hospitals there were occasional cases of extensive and even fatal surface burns in which there was little or no evidence of involvement of the respiratory tract. These discrepancies could usually be explained by the peculiar circumstances in the individual cases.[2a]

As far as could be determined, all the patients who manifested evidence of pathologic conditions in the respiratory tract at any time during their stay in the hospital had definite symptoms of such involvement during the first twenty-four hours. In some cases, to be sure, the symptoms increased in severity after that time. It seems reasonable to suppose, however, that the management of the early phase of the treatment, when shock was present or imminent in many of the cases, had a significant effect on the subsequent course and possibly influenced the severity of the pulmonary symptoms and even the final outcome in some of the cases.

There were considerable interest and concern among the workers here during the first few hours about the possible effects of the injection of large amounts of fluid, particularly plasma and isotonic solution of sodium chloride, on the pulmonary lesion. It is usually assumed from what has been written concerning the treatment of the effects of pulmonary irritants, particularly in gas warfare, that bloodletting is the proper procedure to use in the treatment of pulmonary edema

resulting from such irritants. That seemed reasonable in some ways, although the exact physiologic mechanism involved is not clear. With respect to many of the present patients, however, the possibility that pulmonary edema was present or might develop was clearly overshadowed by the presence of unmistakable evidence of shock. To such patients saline solution and plasma were given freely, and the fluids seemed to produce obvious improvement in most instances without any apparent adverse effect on the respiratory symptoms. This encouraged the use of such fluids also for patients with predominantly respiratory injury and with only minor surface burns when signs of imminent shock were observed. To a few of the patients, to be sure, it was felt at the time that excessive amounts of saline solution may have been given, particularly before an adequate supply of plasma became available, but this probably did not occur after the first few hours.

It was pointed out elsewhere [2a] that evidence of frank pulmonary edema was not made out clinically in the early hours in many cases, unless the scattered crepitant rales heard in many of the very sick patients in the dependent parts of the lungs, and in some instances in other parts of the lungs as well, were the manifestations of such edema. In some patients, who were obviously dying, the tracheal rales and frothy exudate in the mouth were considered to be terminal events, which yielded to no form of treatment that was offered. Measurements of venous pressure or of the oxygen saturation of the blood unfortunately were not made. However, considerable degrees of engorgement of the cervical veins, suggesting increased venous pressure, were not seen except during the period of acute anoxia, when the patients were noticeably excited and dyspneic as a result of obvious obstruction to respiration.

Because of the great interest in this phase of the early management of the cases, the total amounts of the various forms of fluid actually given and recorded in each case are listed in tables 1 and 2 together with the extent of the patient's surface burn and the grade of the severity of the respiratory symptoms. These tables include data on all of the patients admitted to the wards of the Boston City Hospital from the Cocoanut Grove fire except on those who had slight or no surface burns or respiratory symptoms and on 2 patients who died before fluids could be given.

The data concerning the fluid balance were also of prime interest in the first day because of the necessity of there being a good output of urine if sulfonamide therapy were to be used—and it seemed desirable to institute such therapy as early as possible. This aspect as well as other phases of the emergency treatment, such as the use of oxygen,

Data for 28 patients with few or no burns and with little involvement of the respiratory tract are omitted.

Case No.	Sex	Age	Burn, per Cent of Body Surface	Grade of Respiratory Involvement (Clinical)	Fluid Intake, Liters Parenteral Plasma,* Units	0.85% NaCl	5 or 10% Dextrose	Oral Fluids	Urine Output	Day of Discharge
1	F	30	7	3	4	1.0	0	0.3	0.4	16
3	F	20	1	3	6	1.5	0	...†	...	15
4	F	33	6	2	4	0	1.5	0.2	0.7	96
5	M	21	6	1	3	1.5	0	1.3	0.9	25
6	M	44	6	1	2	1.5	0	1.2	0.8	39
8	M	22	4	3	10	4.5	0	2.3	1.5	23
9	M	26	5	2	8	1.5	0	2.3	1.3	20
10	F	22	3	2	3	3.0	0	...	0.3	15
11	M	39	16	3	10 (1)	0	1.5	1.4	1.5	35
12	F	22	1	2	4	0	0	0.3	1.0	24
13	M	24	2	2	3	1.5	0	0.5	0.3	11
14	F.	30	4	2	2 (1)	1.5	0.5	0.9	0.5	24
15	F	30	20	1	4	0.5	0	...	...	197
16	F	20	2	3	3	2.5	0	...	0.7	15
17	F	30	30	2	7	3.0	0	1.0	0.5	200
18	M	26	3	0	1 (2)	1.5	1.5	1.5	0.5	36 hours‡
19	M	23	6	3	10	2.0	0	0.9	0.6	69
20	F	25	0	1	3	0	0	0.5	0.4	4
21	M	25	6	2	14	1.5	0	1.2	1.6	13
22	M	35	6	3	13 (2)	0	0	1.4	1.4	31
23	F	30	10	2	4	4.5	0	0.3	0.9	125
24	M	26	14	3	14	1.5	0	2.2	2.5	130
26	M	20	5	1	3	1.5	0	0.8	1.3	20
27	F	41	0	1	5	0	0	5.3	4.5	8
28	F	27	25	1	6	2.5	1.5	1.2	0.8	87
29	F	38	5	2	6	3.0	0	0.4	0.4	36 hours‡
30	M	30	4	2	7	1.5	0	1.6	1.2	18
31	M	33	3	1	4	1.4	0	0.6	0.6	14
34	M	35	2	1	2	1.5	0	...	...	11
35	M	25	5	2	16	1.0	0	4.2	2.4	25
36	M	34	3	1	2	1.5	0	3.8	1.1	13
37	M	25	6	3	9	1.5	1.5	...	1.1	17
38	M	22	55	2	17	1.5	1.5	2.0	1.6	365
39	M	33	8	1	6	1.5	0	0.3	0.4	28
41	M	22	1	2	0	0	0	0.8	...	11
43	M	25	5	1	0	1.0	0	1.3	0.3	10
47	F	23	0	3	8	0.8	0	0	0.2	18
49	F	28	25	3	12	4.5	0	...	1.9	120
50	F	22	2	2	6	0	0	0.1	...	14
51	F	17	28	2	5	0	0	0.2	...	155
52	F	23	2	3	6	3.0	0	...	...	17
53	M	28	1	3	7	0	3.0	0.8	2.1	11
54	F	28	10	1	4	0.5	0	0.2	0.2+	120
55	F	23	5	0	2	1.0	0	...	...	14
56	M	49	2	1	0	0	0	1.0	0.7	9
57	M	21	3	1	2	0	0	0.9	0.7	14
58	F	28	13	2	17	0.7	0	0.5	0.4	145
59	F	30	8	1	1	1.5	0	...	...	113
60	M	25	4	1	1	0	0	...	...	8
61	M	32	6	2	11	1.5	0	2.3	1.7	58
62	F	29	6	1	5	3.0	1.5	...	...	61
63	F	37	5	1	0	0.7	0	1.9	1.5	7
64	F	22	3	3	1	3.0	0	0.3	0.3	19
65	F	22	6	3	6	3.0	0	...	...	67
66	F	23	1	2	4	0	0	0.7	0.2	31
67	M	23	11	1	11	1.5	0	1.7	1.2	18
68	M	21	5	0	11	1.5	0	1.0	0.9	68
69	M	26	6	3	5	1.5	0	1.2	1.4	24
70	M	36	2	3	2	1.5	0	0.2	0.5	10
86	M	57	6	2	1	3.0	0	0.1	1.3	15 hours‡
89	M	25	2	0	1	1.5	0	...	...	12 hours‡
90T§	F	17	5	4	6	1.5	0	...	...	66
91T	M	50	6	4	7 (1)	5.0	0	0.3	1.4	20
92T	F	32	0	4	2	1.5	0	0.2	0.7	23

* Parentheses enclose additional number of units of albumin. One unit of albumin is equivalent to 100 cc. of a 25 per cent solution, or the osmotic equivalent of 2 units of plasma.

† Leaders indicate that data are not available.

‡ Tranferred to another hospital.

§ T = tracheotomies.

datives and stimulants, is considered elsewhere.[5]   The effects of
e plasma and other fluid intake in combating shock are considered
sewhere by Dr. Lund and Dr. Taylor and their associates.[4]

A total of 693 units of plasma, each consisting of 250 cc., and 17
uits of albumin, each containing 25 Gm. in 100 cc. of water, were

TABLE 2.—*Fluid Balance During First Twenty-Four Hours and Other Relevant Data in Fatal Cases*

Data for 2 patients who died in less than three hours without receiving fluids or plasma are omitted.

Case No.	Sex	Age	Burn, per Cent of Body Surface	Grade of Respiratory Involvement (Clinical)	Plasma,* Units	0.85% NaCl	5 or 10% Dextrose	Oral Fluids	Urine Output	Death, Time after Fire
T†	M	28	5	4	8 (1)	0	7.0	0	1.0	31 hours
T	F	25	25	4	9	0	3.0	...‡	...	25 hours
T	F	22	60	4	8	1.2	0	0.1	0.8	28 hours
T	M	50	6	4	4	0	0	...	...	9 hours
T	M	44	5	4	9	1.5	0	...	0.2	16 hours
T	F	43	<1	4	4	1.5	1.0	...	...	78 hours
T	F	25	20	4	6	1.5	0	...	...	6 hours
T	M	30	13	4	18	1.5	1.0	...	...	24 hours
T	F	22	14	4	10	0	4.5	...	...	34 hours
T	F	22	65	4	10 (3)	3.5	0	1.4	0.8	30 hours
T	F	31	4	4	8	0	1.5	...	0.8	15 hours
T	F	19	?	4	6	3.0	0	0.5	1.8	4 days
T	F	27	15	4	4	3.0	0	...	...	17 hours
T	F	23	35	4	11	0.5	0	4.5	0.8	50 hours
T	F	45	12	4	7	4.5	0	1.0	0.6	7 days
	M	29	65	3	2	3.0	0	...	...	6 hours
	F	22	30	2, A0§	16	1.5	0	...	...	157 days
	M	19	30	2, A4	10	0	0	3.3	0.5	28 days||
	M	41	60	3	17	0	2.5	...	0.4	24 hours
	F	22	30	3	13 (3)	1.0	0	2.0	0.6	9 days
	F	24	30	3	6	0	0	...	...	10 hours
	F	33	65	3	10	1.5	0	...	1.1	29 hours
	M	31	30	4	7	1.5	0	...	0.1	24 hours
	M	42	40	2	3	0	0.5	...	...	4 hours
	M	21	4	4	3	0	0	...	...	7 hours
	M	25	45	4	7 (2)	1.5	1.0	0.7	0.8	5 days
	F	29	65	4	20	0.5	2.5	1.5	0.8	79 hours
	F	54	8	4	10	1.5	0	...	0.8	38 hours
	F	23	0	4	9	1.5	1.0	...	0.4+	25 hours
	M	31	10	4	12 (1)	2.0	0	0.4	1.3	43 hours
	M	25	45	4	7	4.2	0	...	0.2	6 days
	M	50	55	4	12	3.0	2.0	1.8	0.4	42 hours
	F	35	60	1, A3	22	2.0	0	...	0.3	9 days
	M	34	30	0	7 (1)	1.5	0	3.0	0.6	80 days
	M	53	8	4	2	1.5	0	...	...	4 hours
	M	26	45	3	4	0	0	...	...	12 hours
	F	29	45	3, A4	11	3.0	1.5	0.8	0.2	13 days

* Parentheses enclose additional number of units of albumin. One unit of albumin is equivalent to 100 cc. of a 25 per cent solution, or the osmotic equivalent of 2 units of plasma.
† T = tracheotomies.
‡ Leaders indicate that data are not available.
§ A0, A3 and A4 indicate grade of involvement of the respiratory tract observed at autopsy.
|| Patient spent last six days at another hospital.

ven to 98 of the patients.   If one considers each unit of albumin as
e osmotic equivalent of 500 cc. of plasma, the average amount of plasma

5. Finland, M.; Davidson, C. S., and Levenson, S. M.: Chemotherapy and Control of Infection Among Victims of the Cocoanut Grove Disaster, Surg., Gynec. Obst. **82**:151-173, 1946; footnote 2a.

and albumin used in these 98 patients was the equivalent of 7.4 units, or 1,850 cc. of plasma. In addition, a total of 149 liters of 0.85 per cent sodium chloride solution, some of which also contained 5 per cent of dextrose, was given intravenously to 77 of the patients. Only 3 liters of this total was given to patients, 3 in number, who received no plasma. Thus 74 patients received an average of 2 liters of saline solution intravenously in addition to plasma during the first twenty-four hours after the fire. Still more fluids of various kinds were taken orally by most of the patients, and a number of them received intravenous injections of 5 or 10 per cent solutions of dextrose in distilled water. It is not unlikely that still more of the various forms of fluids were given to others and even to some of the same patients and that records of the fact were not made or were lost.

TABLE 3.—*Summary of the Fluid Intake in the Cocoanut Grove Victims During the First Day: Arranged According to the Grade of Severity of the Respiratory Complication*

| Grade of Respiratory Involvement | Number of Cases in Group | Plasma | | Intravenous Sodium Chloride, 0.85% Solution | | Other Fluids * | |
		Number of Cases	Average Number of Units per Patient	Number of Cases	Average Amount, Liters	Number of Cases	Average Amount, Liters
0	24 (1)†	8 (1)	4.4 (9)	7 (1)	1.4 (1.5)	5 (1)	1.8 (3.5)
1	33 (1)	20 (1)	6.3 (22)	18 (1)	1.5 (2.0)	19	1.8
2	19 (3)	18 (3)	7.0 (9.7)	12 (1)	2.1 (1.5)	16 (2)	1.1 (1.9)
3	25 (7)	24 (7)	8.4 (10)	18 (4)	2.2 (2.1)	15 (3)	1.6 (2.3)
4	30 (27)	28 (25)	8.5 (8.8)	22 (19)	2.1 (2.1)	18 (16)	2.1 (2.3)
All groups	131 (39)	98 (37)	7.4 (9.5)	77 (26)	1.9 (2.0)	73 (22)	1.6 (2.3)

* Presumably almost all of the fluids given intravenously, which consisted mostly of 5 per cent or occasionally 10 per cent dextrose solution, are included here and all of the isotonic solution of sodium chloride given parenterally is included in the preceding columns. Satisfactory records of the fluids taken orally were kept only in a minority of the cases, and the amounts taken by the remaining patients are not included in this column. Many of the latter, however, were patients who were discharged to other hospitals or who died during the first day.

† The parentheses enclose the figures for the fatal cases alone.

A summary of the average amounts of fluids of all sorts, including plasma, that were given to the patients admitted from the fire, is presented in table 3. In this table the cases are arranged according to the severity of the respiratory involvement. It is seen that a smaller proportion of the patients without respiratory symptoms and of those with the milder grades of involvement received these fluids, particularly the saline solution. From this table, however, it is not clear which of the patients within each group received each of the various kinds of fluid. It is desirable to know whether those patients who received large volumes of plasma also received significant amounts of the other types of fluids or whether the latter were reserved for patients for whom plasma was not used or to whom it was given in only small amounts.

The data bearing on this point are shown in table 4. In this table the number of patients receiving various amounts of plasma are shown, and for each group of patients the number receiving saline solution and other fluids and the average amounts of such fluids are given. It is seen that the proportion of patients receiving both saline solution and other fluids actually increased with the amount of plasma used and that the average amount of fluids likewise was greater for the patients who received large amounts of plasma than for those who received none or small amounts, except for the patients who received more than 3 liters.

As might be expected, the amount of plasma given was, generally speaking, based on the rate and quality of the pulse, on the blood pressure and, later in the day, on the hemoglobin and hematocrit values.

TABLE 4.—*Correlation of the Amounts of Solution of Sodium Chloride and Other Fluids Given During the First Day with the Amounts of Plasma Administered During the Same Period*

Plasma		Isotonic Solution of Sodium Chloride		Other Fluids	
Number of Cases	Number of Units	Number of Cases	Average Volume,* Liters	Number of Cases	Average Volume,* Liters
33 (2)†	0	3	1.1	5	1.1
52 (11)	1 to 6	28 (6)	2.6 (2.3)	31 (3)	1.0 (0.7)
32 (18)	7 to 12	24 (13)	2.3 (2.1)	25 (13)	2.3 (2.9)
14 (8)	13 or more	12 (7)	1.3 (1.7)	12 (6)	1.9 (1.9)
131 (39)	7.4 (9.5)‡	77 (26)	1.9 (2.0)	73 (22)	1.6 (2.3)

* Averages exclude those who received none of the fluids in question.
† The parentheses enclose the figures for the fatal cases alone.
‡ Averages.

These in turn were related in a general way to the extent of surface burned. Since most of the patients with extensive surface burns also had severe involvement of the respiratory tract, it would appear that the amount of plasma given was also related to the severity of the respiratory lesions. This is brought out clearly in table 5, in which the number of patients receiving varying amounts of plasma is correlated with the percentage of the body surface burned, on the one hand, and with the severity of the respiratory symptoms, on the other.

It is seen from table 5 that, as the extent of the surface burn increased, fewer of the patients failed to receive plasma therapy and that the average amount given to the others increased with the extent of the surface involved. Likewise, two thirds of the patients without definite respiratory involvement and 39 per cent of those with minor symptoms (grade 1) received no plasma at all, whereas only 1 or 2

of each of the groups of patients with the more severe grades of respiratory damage failed to receive any. And here again, the average amounts of plasma given increased with the severity of the respiratory lesions.

NOTES ON ILLUSTRATIVE CASES

From the point of view of the individual patients, those without burns or with only minor surface burns who received large amounts of plasma are of special interest. A few such patients, who received more than 2 liters of plasma or their equivalent in albumin in addition to other parenteral or oral fluids, and who had burns involving only 6 per cent or less of their body surface, may be considered here. A brief note concerning the intake of fluid and the respiratory symptoms in

TABLE 5.—*Relation of the Amount of Plasma Administered During the First Twenty-Four Hours to: A, the Extent of the Body Surface Burned and B, the Degree of Respiratory Damage*

Units of Plasma *	A. Percentage of Body Surface Burned					B. Degree of Respiratory Damage					Total	
	0	1-4	5-9	10-29	30+	0	1	2	3	4	Cases	Per Cent
0	12 (1)†	17	3	1 (1)	0	16	13	1	1	2 (2)	33 (2)	25
1-4	2	17 (2)	10 (2)	4 (1)	3 (3)	5	11	8 (1)	6 (2)	6 (5)	36 (8)	27
5-8	2	7 (1)	9 (2)	4 (2)	5 (4)	1	5	5	7 (1)	9 (8)	27 (9)	21
9-12	1 (1)	1	7 (2)	5 (2)	7 (7)	2 (1)	1	2 (1)	7 (2)	9 (8)	21 (12)	15
13+	0	0	3	4 (2)	7 (6)	0	3 (1)	3 (1)	4 (2)	4 (4)	14 (8)	12
All cases	17 (2)	42 (3)	32 (6)	18 (8)	22 (20)	24 (1)	33 (1)	19 (3)	25 (7)	30 (27)	131 (39)	100
No plasma: % of cases	71	40	9	5	0	67	39	5	4	7		25
Average ‡	5.4	4.0	6.8	9.2	11.1	4.4	6.3	7.0	8.4	8.5	7.4	

* Includes albumin; 25 Gm. of albumin are equivalent to 2 units of plasma.
† The parentheses enclose the numbers of fatal cases included.
‡ Average number of units of plasma per patient, excluding those who received none.

each of these cases will serve best to exemplify the effects of the large intake of plasma and of other fluid under these circumstances.

One of these patients (case 8) had burns involving only 4 per cent of the body surface and received during the first twenty-four hours a total of 10 units (2,500 cc.) of plasma in addition to 4.5 liters of isotonic solution of sodium chloride intravenously and about 2,300 cc. of fluids orally. During this same period his output of urine was about 1,500 cc. When this patient was first admitted to the ward there were second degree burns on his face and hands, his voice was very hoarse and he was coughing and felt chilly. Crepitant rales were heard at the bases of the lungs, and high pitched musical rales were heard in inspiration throughout both lungs. In the course of the first twenty-four hours his respiratory distress increased slightly, but the physical signs were essentially the same at the end of this period and also on the following morning. This patient later raised copious amounts of green purulent sputum from which type III

pneumococci were identified. In the past he had had severe colds about four times a year, and each one left him with a protracted cough productive of much sputum. As far as it could be ascertained, the large amounts of plasma and other fluids which this patient received did not have any unfavorable effect on the respiratory complication. Certainly no truly "wet lung" resulted from the large intake of fluid in this case.

The burns in case 21 involved an estimated 6 per cent of the patient's body surface and were limited to the face, ears, neck and hands. At the time of admission this patient was restless and uncomfortable from the pain of his burns; his blood pressure was 98 systolic and 55 diastolic, his pulse rate was 108 and his lungs were clear to auscultation and percussion. Within four hours he received 1,500 cc. of isotonic solution of sodium chloride and 7 units of plasma, after which his pulse rate was 126 and his blood pressure rose to 130 systolic and 85 diastolic, and remained at this level. By the end of the first twenty-four hours he had received 7 additional units of plasma and taken about 1,200 cc. of fluids by mouth, and his output of urine for the same period was about 1,600 cc. During this time he remained restless, in spite of sedatives, and his temperature rose to 103.4 F., but except for a slight cough and moderate hoarseness, he experienced no apparent respiratory distress. On the following morning the breath sounds were diminished at the base of the left lung but a roentgenogram taken at that time showed no evidence of pulmonary congestion or edema. The large volume of plasma plus the other fluids given to this patient certainly did not aggravate his respiratory symptoms.

Case 22 was another one with burns involving 6 per cent of the patient's body surface—in this instance including the face, hands, forearms and part of the thoracic wall. On admission this patient had a severe cough productive of black-stained mucoid sputum, and shortly thereafter musical and crepitant rales were heard at the bases of both lungs. Injections of plasma were started at 2 a. m., and he received a total of 3,250 cc., in addition to 50 Gm. of albumin (the equivalent of another liter of plasma), within the first twenty-four hours. There is no record of his having received any other fluids intravenously, although some may have been given, but the patient took 1,400 cc. of fluids by mouth and passed about 1,400 cc. of urine during this time. The blood pressure was 120 systolic and 80 diastolic before the first injection of plasma and remained at this level or slightly higher throughout the first two days. Late in the afternoon of the first day the patient began to have dyspnea and stertorous breathing, and this difficulty increased late that evening, but it improved rapidly after oxygen therapy was started. On the following day the patient had several periods of restlessness and dyspnea, and at these times he coughed frequently and raised moderate amounts of tenacious blood-streaked sputum. He also blew large amounts of similar but crusted material from his nose. Large numbers of pneumococci were found in the sputum. The patient subsequently began to show signs of frank consolidation, which proved to be associated with complete collapse of the left lower lobe. Although in this patient there was severe damage to the upper respiratory tract and bronchopulmonary damage, there is no reason to believe that these lesions were seriously influenced by the plasma and albumin or by the other fluids which he received.

In case 35 there were burns of an estimated 5 per cent of the patient's body surface and involving the face, ears, dorsa of both hands and the lower part of the forearms. At the time of the patient's admission to the ward no abnormal physical signs were made out in the lungs, and the throat was clear. Plasma therapy was started within twenty minutes of his arrival, and by the end of twenty-four hours he received a total of 16 units of plasma and a liter of saline solution intravenously and, in addition, took about 4,200 cc. of various fluids by mouth. His output of urine for this period was 2,400 cc. This patient's blood pressure was 160 systolic and 80 diastolic, and his pulse rate was 100 before the plasma was started. Except for a drop in systolic pressure to 140, there was no striking change during the first twenty-four hours; on the following day there was only a slight cough and tracheitis, and the lungs remained clear to physical examination. Some changes were noted, however, in the roentgenogram taken on the second day. No ill effects could be attributed in this case to the plasma given or to the initial large intake of fluid, at least as far as the pulmonary complication was concerned.

Case 91 is of interest because in this case a large amount of saline solution was used for a patient with a severe bronchopulmonary lesion. The patient was a large, obese man of 50 who had a history of severe hay fever and of a chronic cough productive of much thick mucus. He was just recovering from a severe cold and sore throat at the time of the fire. He had inhaled a large amount of smoke, but his burns were limited chiefly to the face and hands and involved about 6 per cent of the body surface. At midnight, when he first arrived in the ward, he was having repeated chills, was coughing violently and expectorating copious amounts of thick, black-stained sputum. His blood pressure at that time was 150 systolic and 70 diastolic, his pulse 112 and his respirations 28 per minute. Injections of saline solution and of human albumin were soon started, and by mid-afternoon he had received a total of 5 liters of isotonic solution of sodium chloride, 100 cc. of a 25 per cent solution of albumin (or the osmotic equivalent of 500 cc. of plasma) and 1,250 cc. of plasma. During this time he had steadily increasing restlessness, dyspnea and stridor and continued to raise thick masses of black sputum until finally his breathing became completely obstructed and an emergency tracheotomy was required. It was necessary to follow this procedure with frequent bronchoscopic suction because of recurrent obstruction of the air passages below the tube, and artificial respiration was resorted to several times before breathing was restored. There was evidence of considerable moisture throughout both lungs all of that day, but there was little change in the pulse and blood pressure except during the periods when he was struggling and restless because of the anoxia which resulted from intermittent obstruction to respiration. The suction gave considerable relief from the dyspnea each time. In this case, which ended in the patient's recovery, the possibility that the large volume of saline solution, when added to the plasma and albumin, contributed to the moisture in the lungs cannot be ruled out. The chief difficulty, however, obviously was due to the changes in the bronchi, and whatever pulmonary edema may have been present could be attributed mainly to anoxia from this cause.

One other case, number 123, may be mentioned. This patient was semicomatose on admission and had "noisy and labored respirations" at the time. She was

also very hoarse and had a "croupy cough." No surface burns were seen. She lived only twenty-five hours after being brought to the hospital. During this time she received 2,250 cc. of plasma, 1,500 cc. of isotonic solution of sodium chloride and 1,000 cc. of a 5 per cent solution of dextrose in distilled water by the intravenous route, and took a small but unknown quantity by mouth. She voided 400 cc. of urine and was incontinent part of the time. Her systolic blood pressure fluctuated between 84 and 120 mm. and her pulse rate was 150 at first and dropped to 120 beats per minute. Her respiratory distress and stridor increased, and she complained for a while of pain in the chest, but she raised no sputum. Coarse rales were heard throughout both lungs. The tracheal obstruction increased steadily, until breathing finally stopped and could not be restored by artificial respiration. Unfortunately there was no autopsy in this case. The possibility that the large volume of fluid had a deleterious effect on her respiratory symptoms cannot be entirely ruled out but seems unlikely.

The cases cited represent the ones in which the largest volumes of plasma and other fluids were given, considering the limited extent of the surface burns. Some of these patients had minor symptoms of involvement of the respiratory tract, while others had severe injuries; one of them died as a result of these bronchopulmonary injuries. Many other therapeutic measures, including morphine, oxygen and a variety of stimulants, were also used in these cases, of course. Their effects are considered elsewhere.[2a] The chief immediate interest in these cases lies in the fact that it is difficult to attribute any significant part of the respiratory distress or any embarrassment of the circulation to the relatively large amounts of plasma and other fluids used. It cannot be stated categorically, however, that they did not contribute to the inflammatory edema in various parts of the respiratory tract and thus also to the obstructive phenomena that were observed.

COMMENT

The exact cause of the pulmonary lesions in the victims of the Cocoanut Grove fire was not determined. At the time of that disaster, the rapid development and severity of the respiratory symptoms, the diffuse rales heard in the chests of many of the patients and the number of deaths resulting from the pulmonary complications within the first few hours all suggested the possibility of a pulmonary irritant such as phosgene. Interest in that possibility was particularly keen at the time because of the widespread educational campaign then being carried on to acquaint the medical profession and civilian defense workers with the various aspects of gas warfare. In addition there was circumstantial evidence which pointed directly to phosgene as a possible factor. The refrigerant used in the air-conditioning system was probably Freon (dichlorodifluoromethane) which, when exposed to free flame or to very hot surfaces, may decompose and liberate phosgene and hydro-

fluoric acid.[6] An early inspection of the charred remains of the building revealed that the tubing which carried the refrigerant had been severed at a point at which the escaping gas must have been exposed to free flame as it entered the main dining room.[7]

The phosgene theory, as well as others which directly implicated specific poison gases, was discarded after a more complete analysis of the available facts. It seemed more reasonable to assume that the injuries were the result of prolonged exposure to the ordinary gases and fumes which result from the incomplete combustion of the type of furnishings which were to be found in the Cocoanut Grove building. The severity of the injuries seemed to be related to the amount of actual exposure to these fumes and to the flames before the victims got out into the open air. The thick, soot-laden exudate which was found lining the mucous membranes all along the respiratory passages in the fatal case was consistent with that explanation. The symptoms and the roentgenologic and pathologic findings were consistent with a severe laryngotracheobronchitis which, because of the edematous and membranous character of the inflammatory reaction in the tracheobronchial tree, gave rise to obstruction of the air passages, which, in turn, resulted in scattered areas of atelectasis and emphysema.

It is possible, therefore, that the nature of the lesions in the present cases could account for the failure of the large amounts of plasma and other fluids to aggravate the pulmonary symptoms. Indeed this form of therapy may have had a salutary effect on the pulmonary lesion similar to that which it may have on surface burns. From the evidence in the present cases it cannot be stated with any degree of certainty what effect such large volumes of fluid and plasma would have on the pulmonary edema produced by phosgene or by other pulmonary irritants when that is accompanied by extensive surface burns, and especially with "shock" present or impending. Indeed it is not certain that the pulmonary edema of phosgene poisoning, when accompanied by depression of the blood pressure, hemoconcentration and other manifestations of clinical shock, would be aggravated by the administration of proper amounts of plasma and other fluids such as would be indicated in the treatment of shock under other conditions which are not accompanied by pulmonary edema. We are not aware of any convincing evidence to clarify this point, although such evidence may be available but not yet revealed.

6. Holmquist, C. A.: Possible Hazards Resulting from Damage to Refrigerators and Equipment in Case of Bombing, Memorandum M-1746, Office of Civilian Defense, Washington, D. C., 1942.

7. Moulton, R. S.: The Cocoanut Grove Night Club Fire, Boston, Nov. 28, 1942, Boston, National Fire Protection Association, 1943.

SUMMARY AND CONCLUSIONS

The data available concerning the administration of plasma and other fluids to the victims of the Cocoanut Grove fire who were admitted to the Boston City Hospital have been analyzed with particular reference to their effect on complications involving the respiratory tract. When all of these data were considered, and particularly when the effects of the largest volumes given to those who were critically ill were carefully scrutinized, it appeared that pulmonary edema did not occur and that the respiratory complications, in general, were not aggravated as a result of this therapy as it was carried out in these cases.

Dr. Charles C. Lund and the other members of the hospital staff granted us permission to study these cases, and Dr. F. H. Laskey Taylor assisted in the study.

HYPERACTIVE CARDIOINHIBITORY CAROTID
SINUS REFLEX

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LOS ANGELES

IT has been known for many years that pressure on the neck over the carotid artery produces slowing of the heart. Parry[1] in 1799 described a retardation of the heart in man by pressure over one carotid artery. Waller[2] in 1862 made similar observations. Czermack[3] in 1866 attributed the slowing of the heart to mechanical stimulation of the vagus nerve. Many observations were reported on the effects on the cardiac mechanism of pressure over the carotid sheaths, and the test was called the vagus pressure test. It was not until 1927, with the publication of Hering's excellent monograph,[4] that it was definitely demonstrated that the vagus nerve was not affected directly but that pressure over the carotid sheath stimulated sensory endings in the carotid sinus, which resulted in reflex cardiac inhibition and other reflex effects.

The brilliant investigations of Hering,[4] Heymans[5] and Koch[6] established the function of the carotid sinus in man. The possibility that abnormal stimulation of the carotid sinus mechanism might give rise to symptoms has been suggested in several reports. Prior to the discovery of the carotid sinus reflex Czermack[3] (1866) noted in himself that pressure over the right side of the neck was liable to cause dizziness and faintness. Hering[4] in his monograph suggests that death from hanging and the knockout blow in the neck, in boxing, might

1. Parry, C. H.: An Inquiry into the Symptoms and Causes of Syncope Anginosa, Commonly Called Angina Pectoris, Bath, R. Cuttwell, 1799.

2. Waller, A.: Experimental Researches on the Functions of the Vagus and the Cervical Sympathetic Nerves in Man, Proc. Roy. Soc., London 11:302, 1862.

3. Czermack, J.: Ueber mechanische Vagus-Reizung beim Menschen, Jenaische Ztschr. f. Med. u. Naturw. 2:384, 1866.

4. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe, Dresden, Theodor Steinkopff, 1927.

5. Heymans, C.: Le sinus carotidien et les autres zones vasosensibles réflexogènes, London, H. K. Lewis & Co., Ltd., 1929.

6. Koch, E.: Die reflektorische Selbsteuerung des Kreislaufes, Dresden, Theodor Steinkopff, 1931.

be the result of stimulation of the carotid sinus. Gaisbeck [7] (1928) observed fainting and convulsions associated with a hyperactive carotid sinus reflex. Roskam [8] in 1930 described a 52 year old patient who suffered severe and frequent attacks of unconsciousness and convulsions. He demonstrated that pressure over the carotid sinus or stretching the skin over the sinus as in shaving would induce an attack. It was Weiss and Baker [9] (1933), however, who brought wide attention to the clinical significance of the hyperactive carotid sinus reflex. These observers, studying a large group of patients with symptoms of fainting and convulsions and related symptoms, found 15 in whom pressure on the carotid sinus reproduced the symptoms. They described in detail the features of the carotid sinus syndrome. The efferent effects of the carotid sinus sensitivity were divided into three types: (1) cardiac, (2) depressor, and (3) cerebral. The observations of Weiss and Baker have been confirmed by others, and the syndrome is now well established.

In patients whose attacks are frequent and disabling, surgical denervation of the carotid sinus has been performed. The relief of symptoms has not been uniformly successful, and therapeutic failures and incomplete cures have been reported.[10] Favorable results would be anticipated (a) if in all cases the clinical manifestations were due solely to the hyperactive carotid sinus mechanism and (b) if in all instances surgical therapy eliminated the hypersensitive portion of the reflex. Therapeutic failures could be explained by either (a) an improper evaluation of the significance of an abnormal response to carotid sinus stimulation leading to errors in diagnosis or (b) an incomplete understanding of the site of hypersensitivity of the hyperactive reflex resulting in the failure of surgical measures to eliminate the underlying pathologic condition.

In the course of pharmacologic studies on the carotid sinus [11] the sensitivity of the reflex was tested routinely over a period of years.

7. Gaisbeck, F., cited by Koch.[6]

8. Roskam, J.: Un syndrome nouveau syncopes cardiaques graves et syncopes répétées par hyperréflectivité sino-carotidienne, Presse méd. **38**:590, 1930.

9. (a) Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, Medicine **12**:297, 1933. (b) Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, ibid. **14**:377, 1935.

10. (a) Weiss, S.; Capps, R. B.; Ferris, E. B., Jr., and Munro, D.: Syncope and convulsions Due to a Hyperactive Carotid Sinus Reflex, Arch. Int. Med. **58**:407 (Sept.) 1936. (b) Craig, W. M., and Smith, H. L.: The Surgical Treatment of Hypersensitive Carotid Sinus Reflexes, Yale J. Biol. & Med. **11**:415, 1939.

11. Nathanson, M. H.: Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch. Int. Med. **51**:387 (March) 1933; Further Observations on the Effect of Drugs on Induced Cardiac Standstill, ibid. **54**:111 (July) 1934.

A large number of persons were found who exhibited a pronounced cardiac inhibition on stimulation of the carotid sinus. From this material the following studies were carried out, first, an analysis of the incidence of the carotid sinus syndrome in persons who exhibit a hyperactive response and, second, a study of the site of hypersensitivity of the hyperactive reflex.

INCIDENCE OF THE CAROTID SINUS SYNDROME IN PERSONS WITH A HYPERACTIVE CARDIOINHIBITORY REFLEX

Procedure.—The observations were carried out on ambulant patients who were tested routinely by mechanical stimulation of the carotid sinus. Although both sinuses were frequently tested, the present observations include the response to pressure on the right carotid sinus only, since this usually elicited the more pronounced cardiac inhibition. In the literature the meaning of a hyperactive cardioinhibitory response is frequently rather vague. Some published records show only a moderate cardiac inhibition, interpreted as a hyperactive reaction. In the present study the following were considered as the requirements for a hyperactive response: (1) a cardiac standstill of at least five seconds' duration, (2) cardiac inhibition induced by simple pressure on the carotid sinus without massage of the sinus, and (3) a standstill of equal intensity elicited on several tests. The last was included because in some persons a hyperactive response could be obtained on the first application of pressure; however, the reflex apparently became easily refractory, as on a second application of pressure the intensity of response was greatly diminished. Such reactions were not included in this series.

Of those persons from whom a hyperactive cardioinhibitory response was obtained a careful history was taken with special reference to symptoms considered characteristic of the carotid sinus syndrome. Inquiry was especially made concerning such symptoms as attacks of syncope, convulsions, faintness and dizziness.

The patient was questioned concerning the influence on the development of symptoms of position of the body, movements of the head and neck and pressure on the neck by constricting neckwear. When suggestive symptoms were elicited, the pressure on the carotid sinus was repeated, and a comparison was made of the induced symptoms and those of the spontaneous attacks.

Results.—A cardiac standstill fulfilling the criteria mentioned was induced in 115 patients. The youngest was 30 years and the oldest 81 years of age, the average age being 58.9 years. Table 1 shows the age distribution by decades. There were 98 men and 17 women in this group. The greater frequency of cardiac *inhibition with age*

has previously been observed (Gilbert,[12] Sigler [13] and Nathanson [14a]). The greater frequency and intensity of the cardiac response in men has also been reported.[14]

Of the 115 patients exhibiting a hyperactive cardioinhibitory reaction 77, or 67 per cent, presented no symptoms suggestive of the carotid sinus syndrome. Of the remaining 38 patients there were 23 whose reactions could be classified as instances of the carotid sinus syndrome with a fair degree of certainty. In 10 patients the manifestations of the carotid syndrome were the chief complaints, while in the remainder these symptoms were secondary and of relatively mild degree. Attacks of syncope were experienced by only 6 patients. Attacks of sufficient severity and frequency to cause serious disability were experienced by only 4. In 1 patient denervation of the left carotid sinus was performed.

The symptoms in most instances were described as attacks of sudden weakness, dizziness or faintness. The sensations were usually

TABLE 1.—*Age Distribution of 115 Patients with a Hyperactive Cardioinhibitory Carotid Sinus Reflex*

Age, Years	Number of Patients
30 - 40	4
40 - 50	14
50 - 60	37
60 - 70	44
70 - 80	15
80 - 90	1

related to changes of position of the body or head. Two patients experienced the symptoms while straining at stool. In each case the subjective sensations were reproducible by pressure on the carotid sinus.

Of especial interest is the group of 15 persons who presented symptoms resembling those of the carotid sinus syndrome but who were excluded for the following reasons: First, some mechanism other than the hyperactive carotid sinus reflex could be demonstrated as a basis for the attacks, and second, the spontaneous attacks did not resemble the symptoms produced by pressure over the carotid sinus. In 5 persons there as a true vertigo associated with nausea and tinnitus, indicative of Ménière's syndrome. The sensations

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12. Gilbert, N. C.: The Increase of Certain Vagal Effects with Increased Age, Arch. Int. Med. **31**:423 (March) 1923.

13. Sigler, L. H.: Clinical Observations on the Carotid Sinus Reflex, Am. J. M. Sc. **186**:118, 1933.

14. (*a*) Nathanson, M. H.: Rhythmic Property of the Human Heart, Arch. Int. Med. **72**:613 (Nov.) 1943. (*b*) Sigler, L. H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex, Arch. Int. Med. **67**:177 (Jan.) 1941.

following pressure on the carotid sinus had no similarity to the sensations at the time of the spontaneous attacks.

In 4 patients the symptoms of faintness and dizziness were associated with attacks of paroxysmal tachycardia. Two persons suffering anginal attacks noted that a sensation of faintness followed the use of glyceryl trinitrate.

One patient is of particular interest in that he had two types of manifestations, (1) attacks of faintness which could be reproduced by pressure on the carotid sinus and (2) attacks of severe vertigo apparently due to Ménières syndrome, which could not be induced by stimulation of the carotid sinus. For 4 persons the diagnosis was neurosis, and the symptoms induced in them did not resemble the spontaneous attacks.

COMMENT

It is apparent that a large proportion of persons possessing a hyperactive cardioinhibitory reflex of the carotid sinus do not exhibit
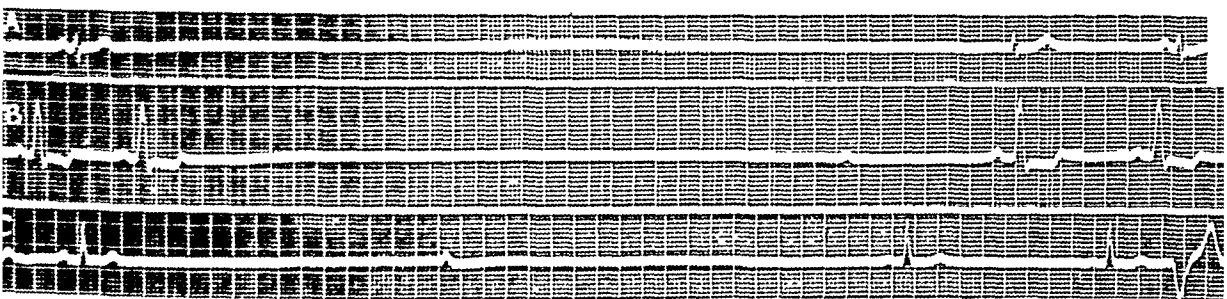
Fig. 1.—*A*, electrocardiogram of patient I. W. showing a cardiac standstill of 8.2 seconds easily induced by pressure on the right carotid sinus. The patient had no symptoms suggestive of the carotid sinus syndrome. *B*, electrocardiogram of patient J. W. showing the effect of pressure on the right carotid sinus for 3 seconds, ventricular standstill of 7.6 seconds induced. The patient had coronary disease but presented no symptoms indicative of cerebral ischemia. *C*, electrocardiogram of patient J. L. showing a ventricular standstill of 7.2 seconds induced by pressure over the right carotid sinus. The patient did not exhibit any symptoms indicative of the carotid sinus syndrome.

the manifestations of the carotid sinus syndrome. A definite distinction must thus be made between the hyperactive carotid sinus reflex, which designates a hyperactive response to stimulation of the carotid sinus, and the carotid sinus syndrome, which designates a clinical condition. There is no satisfactory explanation for the absence of symptoms in many persons and the presence of symptoms in others. The cardiac inhibition was as intense and as easily elicited in the asymptomatic group as in those presenting symptoms (fig. 1). Many persons in whom a prolonged cardiac arrest could be induced consistently with remarkable ease tolerated sudden movements of the head and body and tight neckwear without the slightest discomfort.

A variation in sensitivity to cerebral ischemia might be considered as a possible explanation. It is conceivable that cerebral ischemia is better tolerated by some persons than by others. Such a variation in reaction was noted in the present study. A prolonged cardiac standstill was induced in many instances with relatively minor subjective and objective reactions. In other persons faintness and dizziness followed a cardiac inhibition of only a moderate degree. However, there was no apparent difference as regards the tolerance to the induced cardiac arrest in the group presenting symptoms as compared with the asymptomatic group.

The following is offered as a reasonable explanation for the variation in clinical manifestations in persons who possess a hyperactive reflex of the carotid sinus. The sensory receptors in the carotid sinus are located in the adventitial layer. In this position they are easily accessible to external pressure such as is applied in the carotid sinus test. The ease with which a cardiac standstill and the associated symptoms may be induced by pressure on the sinus is apparently responsible for the general impression that the spontaneous attacks are also induced by external pressure. Weiss and his associates [9] have emphasized such factors as pressure from a tight collar, a blow over a sensitive sinus and changes in position of the head in precipitating attacks. However, these observers stated that in only a few cases did the history clearly indicate a mechanical stimulation of the sinus as a cause of spontaneous syncope. In the present study a definite history suggesting the influence of external pressure was noted for only 1 patient. The symptoms were usually precipitated by a change in the position of the body or a sudden movement of the head. It need not be assumed that such movements stimulate the sensory receptors in the sinus by external compression, since changes in the intravascular pressure may also be brought about in the same manner. The pressure within the carotid sinus, the intrasinal pressure, is the normal physiologic stimulus, and changes in this pressure are transmitted to the sensory receptors. The fact that a history of mechanical stimulation as a cause of spontaneous attacks is infrequent suggests that symptoms result from variations in intravascular pressure rather than from variations in external pressure. The activity of the reflex as elicited by external pressure (the carotid sinus test) is not necessarily an exact measure of the intensity of the response to variations in intrasinal pressure. Sunder-Plassman [15] and Keele [16]

15. Sunder-Plassman, P.: Untersuchungen über den Bulbus carotidis bei Mensch und Tier im Hinblick auf die "Sinusreflexe" nach, H. E. Hering, Ztschr. f. d. ges. Anat. (Abt. 1) **93**:567, 1930.

16. Keele, C. A.: Pathological Changes in Carotid Sinus and Their Relation to Hypertension, Quart. J. Med. **2**:213, 1933.

have shown that arteriosclerotic changes are likely to be pronounced and to occur early in the carotid sinus. It is a definite possibility that the structure of the carotid sinus in some persons is such that changes in intrasinal pressure are easily transmitted to the sensory endings, resulting in cardiac inhibition and the associated symptoms. In other persons (the asymptomatic group) structural abnormalities may be present in the sinus which, acting as a block, prevent variations in intrasinal pressure from stimulating effectively the sensory receptors in the adventitial layer. Spontaneous attacks would occur only in those persons in whom the hyperactive response is elicited by an increase in both external and internal pressure. These variations in the mechanism of the carotid sinus are suggested as a possible explanation for the difference in clinical manifestations in persons who possess a hyperactive carotid sinus reflex.

The realization that a hyperactive carotid sinus reflex may be only incidental and of no clinical significance is of practical importance. An appreciation of this fact will prevent errors in diagnosis and treatment. Four patients of the present series had previously received the diagnosis of carotid sinus syndrome, primarily because a hyperactive carotid sinus reflex could be elicited. Denervation of the carotid sinus was considered. On further study, 1 patient having attacks of amnesia and confusion was found to be suffering from a severe psychoneurosis, and for the other 3 patients the diagnosis was Ménière's syndrome. An important diagnostic point is the ability to reproduce symptoms of the spontaneous attacks by pressure on the carotid sinus. If the induced symptoms do no simulate the spontaneous attacks, some other mechanism should be looked for as a basis for the clinical condition. It is very possible that some of the unsatisfactory results following surgical treatment of the carotid sinus syndrome are due to an uncritical selection of patients.

The Site of Hypersensitiveness of the Hyperactive Cardioinhibitory Reflex.—Early investigators of the carotid sinus reflex [17] attributed the hyperactive response to hypersensitivity of the sensory receptors in the sinus. They concluded that local sclerotic changes were important in that mechanical pressure on a sclerotic plaque would result in a more intense stimulation of these receptors. A hyperirritability of the afferent receptors caused by ischemia of the neural endings subsequent to vascular sclerosis was also considered. More recently Koffler and Alexander [18] also concluded that calcareous deposits in the wall of the carotid artery were responsible for the exaggerated reaction.

17. Hering.[4] Heymans.[5] Koch.[6]

18. Koffler, A., and Alexander, S. F.: Hyperactive Carotid Sinus Reflex Syndrome, New York State J. Med. **40**:1519, 1940.

There is some evidence that the site of hyperirritability may be in other portions of the reflex pathway. Weiss and his associates [9] emphasized the importance of local lesions in or about the sinus. However, these observers also made the following statement: "In the hyperactive state of the reflex, the condition of the efferent end organs as well as the afferent end organ, i. e. the morphological condition of the sinus, plays an important role."

The participation of the efferent end organ, the heart, in the hyperactive response is suggested by several investigations. Before the discovery of the carotid sinus reflex the cardiac slowing which followed pressure over the carotid artery was attributed to direct stimulation of the vagus nerve. The hyperactive response was explained as due to increased sensitivity of the endings of the vagus nerve resulting from pathologic changes in the heart. An exaggerated cardiac response to "vagus pressure" in heart disease was observed by Wenckebach and Winterberg,[19] Daniélopolu and Missirlin,[20] Braun and Samet [21] and others. Braun and Samet [21] also demonstrated an exaggerated cardiac inhibition on stimulation of the vagus nerve in cats following ligation of the left coronary artery. Weiss and Baker [9n] stated that "patients with coronary disease tended to exhibit marked slowing of the heart" on stimulation of the carotid sinus. Sigler [14b] concluded that coronary disease was the condition in which the reflex occurs with the greatest frequency and the highest degrees of response. These observations suggest that the efferent limb of the reflex may be implicated in the hyperactive response.

<div style="text-align:center">METHOD AND OBSERVATIONS</div>

In the present study an attempt was made to determine the site of hypersensitivity of the hyperactive cardioinhibitory reflex by a method previously described.[22] The previous report was limited to observations on 1 patient, while in the present study the method was applied to a larger group. The basis of the method is the following: Hering [4] has demonstrated that pressure on the carotid sinus elicits two independent effects; (a) a cardioinhibitory effect and (b) a

19. Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927.

20. Daniélopolu, D., and Missirlin, V.: Excitabilité centrifuge du vague dans les hypertonies générales et les lésions chroniques du coeur: valeur diagnostique et pronostique de l'épreuve du vague dans ces affections, Compt. rend. Soc. de biol. **92**:538, 1925.

21. Braun, L., and Samet, B.: "Vagusdruck" und Koronargefäss: (Ein klinischer und experimenteller Beitrag zur Diagnose und Prognose der Herzkrankheiten), Deutsches Arch. f. klin. Med. **161**:257, 1928.

22. Nathanson, M. H.: Site of Hypersensitiveness of the Exaggerated Sinus Caroticus Reflex, Proc. Soc. Exper. Biol. & Med. **29**:1037, 1932.

vasodepressor effect. The sensory receptors in the carotid sinus and the afferent nerve pathways are the same for both reflexes. There are, however, two separate efferent pathways by way of the vagus nerve to the heart (cardioinhibitory effect) and by way of vasomotor fibers to the blood vessels (vasodepressor action) (fig. 2). The cardiac effect may be eliminated by atropine and the vascular reaction independently observed. Since the afferent endings are common to both reflexes, a pronounced cardioinhibitory effect may be explained by a hypersensitiveness of the afferent receptors if there is likewise a vascular reaction of a comparable degree. On the other hand, the combination of a pronounced cardiac inhibition and a mild effect on blood pressure is strong evidence that the afferent mechanism is not the site of hypersensitivity of the reflex. With this as a basis, persons showing hyperactive cardioinhibitory responses were selected and observations made on the vascular reactions to pressure on the carotid sinus.
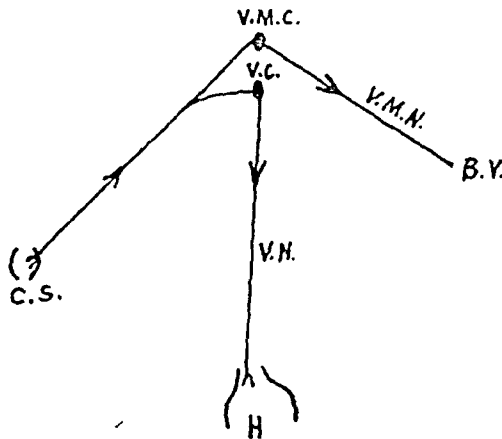
Fig. 2.—Diagram of the carotid sinus reflex pathways. Cardioinhibitory and depressor impulses pass from the receptors in the carotid sinus (*C.S.*) by a common pathway to the vagus (*V.C.*) and vasomotor (*V.M.C.*) centers in the medulla. There are two separate efferent pathways by way of the vagus (*V.N.*) to the heart (*H*), cardioinhibitory reflex, and by way of the vasomotor nerves (*V.M.N.*) to the blood vessels (*B.V.*), depressor reflex.

These observations were carried out on 12 male patients. In each instance a prolonged cardiac standstill of at least six seconds' duration could be elicited repeatedly by pressure on the right carotid sinus. The procedure with each patient was as follows: After the patient had rested in the supine position for fifteen minutes, several readings of the systolic and diastolic blood pressures were made. An electrocardiogram was then taken and the induced cardiac standstill demonstrated graphically. Atropine sulfate, 0.001 Gm., was then administered intravenously. After an interval of five minutes the blood pressure was again taken and the electrocardiogram repeated to determine the effect of pressure on the carotid sinus. In each instance

the cardioinhibitory response was abolished (fig. 3). The depressor reaction could then be observed independently. The blood pressure was then taken before and during the stimulation of the right carotid sinus. Readings were continued until the blood pressure returned to the original levels. Since the degree of reponse depends on the intensity of the stimulus, the duration and intensity of the pressure on the carotid sinus were maintained constant in each experiment. In each instance a fall in systolic pressure followed stimulation of the carotid sinus. The changes in the diastolic pressure were less noticeable. After the administration of atropine, pressure on the carotid sinus produced an average drop in systolic pressure of 15 mm. of
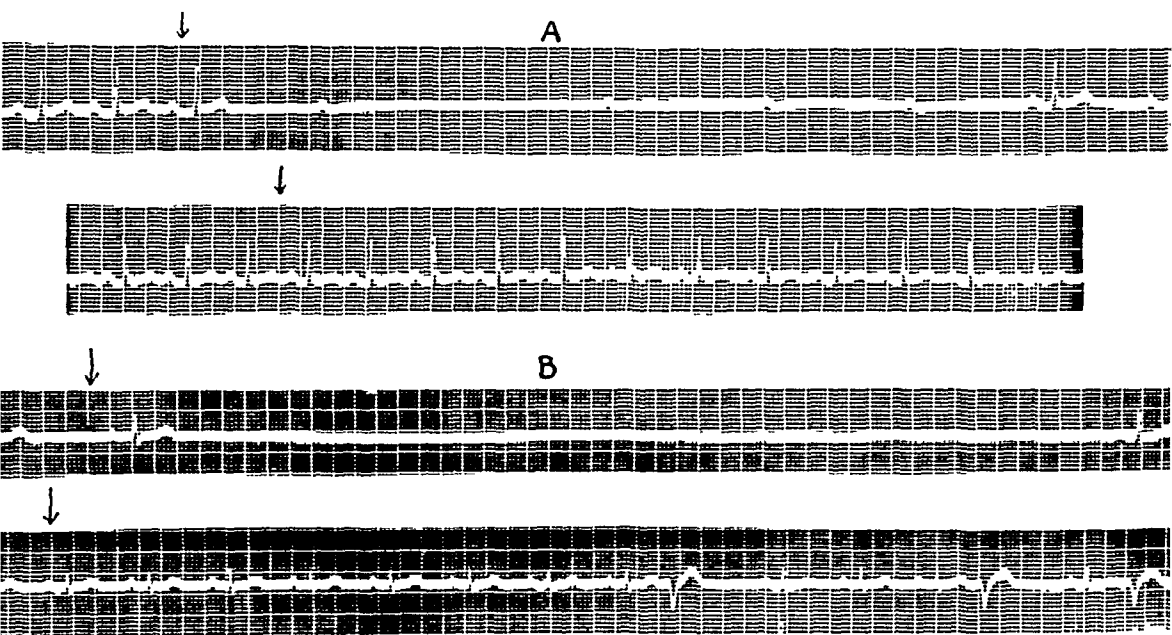
Fig. 3.—A, electrocardiogram of J. L.: Upper strip shows ventricular stand-still of 8 seconds induced by pressure on the right carotid sinus (arrow). Lower strip shows abolition of standstill after administration of atropine sulfate. Pressure on the carotid sinus after the administration of atropine induced a drop in blood pressure of 8 mm. systolic and 6 mm. diastolic.

B, electrocardiogram of L. R.: The upper strip shows cardiac standstill of 9.4 seconds induced by pressure on the right carotid sinus (arrow). The lower strip shows abolition of standstill after administration of atropine sulfate. Pressure on the carotid sinus after the administration of atropine induced a drop in systolic pressure of 14 mm. of mercury. The diastolic pressure was not affected.

mercury and in diastolic pressure of 4.2 mm. of mercury. The results of these observations are shown in table 2.

Various reports in the literature indicate that the depressor reactions observed in the present study cannot be considered abnormal in degree. Tomanek [23] observed a drop in blood pressure of 9 to 12.5

23. Tomanek, Z.: Carotissinusreflex beim Menschen, Klin. Wchnschr. 7:898, 1928.

per cent in normal persons. Mandelstamm and Lifschitz [24] demonstrated an average fall in systolic blood pressure of 37 mm. of mercury in elderly patients. Weiss and Baker [9a] in a group of nonhypersensitive elderly persons found a drop in systolic pressure of from 10 to 65 mm. of mercury, with an average of 30 mm. The average fall in diastolic pressure was 25 mm. It is evident that the depressor responses observed in the present study are mild in degree and not at all comparable in intensity to the cardioinhibitory reactions elicited. These results indicate that the afferent pathway may be excluded as the site of hypersensitivity of the cardioinhibitory reflex.

TABLE 2.—*Blood Pressure Responses to Stimulation of the Carotid Sinus After the Administration of Atropine to Persons Who Have a Hyperactive Cardioinhibitory Carotid Sinus Reflex*

| Patient | Age | Blood Pressure (Before Atropine), Mm. Hg | After Atropine | |
			Before Carotid Sinus Pressure, Mm. Hg	During Carotid Sinus Pressure, Mm. Hg
L. G.	68	118/72	112/60	82/60
L. R.	75	122/84	118/60	104/60
H. K.	65	156/78	140/74	110/62
A. S.	70	116/60	118/62	108/62
H. L.	50	104/72	106/78	100/80
J. S.	72	104/70	102/70	84/62
N. L.	62	120/72	114/70	104/70
L. L.	63	118/82	112/80	102/72
J. B.	68	112/80	120/80	110/68
J. S.	70	130/90	128/90	110/90
J. L.	37	136/74	124/70	116/64
M. P.	62	132/90	130/90	120/78

COMMENT

The afferent pathway having been excluded as the site of hypersensitivity, either the vagus center in the medulla or the efferent path, the vagus nerve, must be considered responsible for the hyperactive response. The evidence strongly favors a hypersensitivity of the vagus nerve. This is supported by the frequent association of a hyperactive carotid sinus reflex with clinical disease of the peripheral end organ, the heart. Also, hyperactivity of the carotid sinus reaction has been produced by experimental damage to the myocardium.[21] In animals and in human beings there is evidence of an increased activity of the vagus nerve with age.[25] It has been shown repeatedly that the cardioinhibitory response to stimulation of the carotid sinus is more frequent and intense in advanced years.[14b,a] An exaggeration of

24. Mandelstamm, M., and Lifschitz, S.: Die Wirkung der Karotissinusreflexe auf den Blutdruck beim Menschen, Wien. Arch. f. inn. Med. 22:397, 1932.

25. Allbutt, C.: Diseases of the Arteries Including Angina Pectoris, London, Macmillan & Co., 1915. Gilbert.[12]

the cardioinhibitory reflex has been observed after the administration of drugs which sensitize the vagus, such as digitalis,[26] and mecholyl (acetyl-beta-methylcholine).[9]

The localization of the site of hypersensitivity of the carotid sinus reflex is of more than theoretic significance. Surgical denervation of the carotid sinus is a method of therapy for patients having symptoms attributed to a hyperactive reflex. Such therapy by eliminating the afferent receptors should result in a permanent cure if the hypersensitivity was in the afferent pathway. However, it might be anticipated that denervation of the carotid sinus would not insure a consistent and permanent cure if the hypersensitivity was predominantly in the vagus nerve. It is true that by this procedure the chief pathway for afferent impulses is removed and the activity of a hypersensitive vagus nerve thus reduced. However, as is well known with other reflexes, the vagus nerve can be reflexly activated from other sites in the body. Weiss and Ferris [27] reported a vasovagal syncope in which impulses originating in a diverticulum of the esophogus reflexly caused sufficient stimulation of the vagus to produce cardiac standstill. They reported other cases in which a similar vagal reflex originated from the bronchi, pharynx, larynx and eyeball. Capps and Lewis [28] observed instances in which vagal reflexes could be induced by irritation of the pleura.

The carotid sinus is thus but one of a number of sensory areas from which reactions of a similar nature may be produced. The patient with the carotid sinus syndrome still possesses a hypersensitive vagus nerve after denervation of the carotid sinus. Reflex vagal stimulation resulting in symptoms may thus persist, although the possibility is lessened by the elimination of a most important source of afferent stimuli. This might well be the explanation for the variable results following denervation of the carotid sinus. Craig and Smith [10b] followed 12 patients with whom this procedure had been carried out. As to elimination of symptoms of the carotid sinus syndrome, the following were the results: 4 excellent, 1 good, 4 fairly good and 3 failures. The fact that after denervation of the carotid sinus the clinical course was frequently unchanged or only slightly modified suggests that a hypersensitive vagus mechanism continued to be activated from other sensory areas.

26. Nathanson.[11] Koch.[6] Weiss and Baker.[9a] Ferris, Capps and Weiss.[9b]

27. Weiss, S., and Ferris, E. B., Jr.: Adams-Stokes Syndrome with Transient Complete Heart Block of Vasovagal Reflex Origin, Arch. Int. Med. **54**:931 (Dec.) 1934.

28. Capps, J. A., and Lewis, D. D.: Observations upon Certain Blood-Pressure-Lowering Reflexes That Arise from Irritation of the Inflamed Pleura, Tr. A. Am. Physicians **22**:635, 1907.

SUMMARY AND CONCLUSIONS

1. A study was made of a group of 115 persons in whom a hyperactive carotid sinus cardioinhibitory reflex was elicited.

2. The hyperactive reflex was more frequent in advanced age and in men.

3. Only a small proportion of the persons with a hyperactive reflex exhibited the manifestations of the carotid sinus syndrome.

4. An explanation is offered for the variation in clinical manifestations among the persons showing a hyperactive carotid sinus reflex.

5. A correct evaluation of the significance of a hyperactive reflex is necessary so that errors in diagnosis and therapy may be avoided.

6. Observations are presented which indicate that hypersensitivity of the vagus nerve is the basis for the hyperactive cardioinhibitory carotid sinus reflex.

7. A hyperactive response of the vagus nerve to stimuli from various sensory areas is suggested as an explanation for some therapeutic failures following denervation of the carotid sinus.

SYSTEMIC INFECTION DUE TO TORULA HISTOLYTICA
(CRYPTOCOCCUS HOMINIS)
I. Report of Four Cases and Review of the Literature

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INDIANAPOLIS

SYSTEMIC infection by Torula histolytica was first clearly recognized by Stoddard and Cutler in 1916.[1] In their exhaustive monograph they reported 2 cases in man and established the criteria for differentiation of Torula histolytica (a term which they introduced) from Blastomycosis hominis and Coccidioides immitis, with which it previously had been confused. The chief means of distinguishing these organisms is by their manner of growth on artificial media; Torula organisms reproduce by budding only; Blastomyces organisms form arthrospores, and Coccidioides organisms form endospores. In clinical practice Torula organisms have been overlooked because of the failure to culture them on suitable media or for sufficiently long periods of time. They have also been mistaken for white blood cells in examination of the spinal fluid. The problem of their identification has been reviewed recently by Holt.[2]

In 1937, Levin[3] reviewed the literature up to that time, summarizing the clinical and pathologic observations. Binford[4] added 14 cases from the literature and his own experience from the time of Levin's review until 1940. In the table these summaries are extended to cover the cases reported from 1940 to the present in accordance with Levin's scheme; they cover a total of 108 cases.

It will be seen that the age incidence of torulosis is rather uniformly distributed over the period of active adult life, and that the disease is approximately twice as frequent in males as in females.

1. Stoddard, J. L. and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916.

2. Holt, R. A.: The Identification of Blastomycoides Histolytica in Three Infections of the Central Nervous System, J. Lab. & Clin. Med. 27:58-62, (Oct.) 1941.

3. Levin, E. A.: Torula Infection of the Central Nervous System, Arch. Int. Med. 59:667-684 (April) 1937.

4. Binford, C. H.: Torulosis of the Central Nervous System: Review of Recent Literature and Report of a Case, Am. J. Clin. Path. 11:242-251 (March) 1941.

The generalized form of infection has increased relatively since the time of Levin's report, and the antemortem diagnosis is being made more frequently. This undoubtedly reflects an increased consciousness of the disease.

Inspection of the figures relative to the duration of the illness and reading of the individual case reports suggest that infections with Torula organisms may follow two courses. The majority of patients will die within six months of the onset of symptoms, but if they survive this initial acute phase they may then live from two to four years. This would suggest that if the patient can overcome the primary attack some form of immunity occurs, or a relative balance between the host and the organism. If this is true, our knowledge up to the present would offer no good explanation for such a phenomenon. Stoddard and Cutler[1] in their original article were unable to demonstrate any consistent response of immunity to the organism. Hoff,[5] in a more recent attempt to produce an immunity in mice by the injection of the killed organisms, could increase their survival time compared to that of normal controls after the injection of virulent organisms; but the inference from his data is that the immunized group all died, also, even though it required a longer period of time. Immunity, if it is considered to be the ability to overcome the disease, has not been demonstrated up to the present time.

Since the involvement of the central nervous system is the most constant feature of systemic torulosis and is invariably the cause of death, the clinical picture is one of a meningitis of slow onset or one of an intracranial neoplasm. Intermittent headache of increasing frequency and intensity is the most frequent initial symptom. This may be followed by vertigo, stiffness of the neck, symptoms of a focal brain lesion, irritability and, ultimately, profound mental disorders. Nuchal rigidity, positive Kernig's sign, ophthalmoplegia and papilledema are the manifestations most constantly observed on physical examination, and focal neurologic signs are frequent. The course is progressively downhill, with a fever seldom above 101 F., to death in coma with respiratory failure. Examinations of the blood and the urine are usually of no diagnostic significance, although the organisms have been obtained in some cases in blood and urine cultures. Examination of the spinal fluid shows it to be under increased pressure; the fluid may be clear, xanthochromic or turbid. The cell counts range from 200 to 800, and there is usually a predominance of lymphocytes. Albumin and globulin are increased, and the sugar may be very low. The organisms may be seen on direct smear as round, gram-positive cells which

5. Hoff, C. L.: Immunity Studies of Cryptococcus hominis (Torula Histolytica) in Mice, J. Lab. Clin. Med. **27**:751-754 (March) 1942.

have doubly refracting walls and reproduce by budding, or they may be found only after culture.

The most constant pathologic lesion found in these cases is the miliary nodule, which both grossly and microscopically resembles a tubercle. In early visceral lesions an abscess consists of an amorphous mass of disintegrating polynuclear and mononuclear white cells and yeast cells surrounded by a loosely organized wall of vascular connective tissue. Throughout the wall is a generalized infiltration of large mononuclear phagocytic cells, which may at times form multinucleate giant cells. In older lesions, whorls of fibroblasts and epithelioid cells surround a homogeneous center in which the yeast cells are ill defined. Giant cells are more frequent at this stage.

In the central nervous system the evidences of tissue reaction are much less. The meninges may show an inflammatory granulomatous process, and the surface of the brain itself may show a zoogleic mass, staining homogeneously and containing numerous yeast cells. In the brain substance monocytic cellular reaction occurs about the larger vessels, suggesting that the organism follows the vessels into the brain, and most parenchymal lesions follow their course. These lesions have the appearance of cysts containing Torula organisms lying free in a cavity of normal brain tissue. Very little if any glial reaction occurs about these cavities.

The mode of infection with Torula histolytica continues to remain obscure. Infections have been reported from all sections of the world and occur in all classes of society. The portal of entry is most probably the lung, as this organ is the second most frequently infected tissue. Thence the infection is probably carried to the other organs by way of the blood and the lymph channels. That it is a true septicemia is further indicated by the work of Wade and Stevenson.[6] When they inoculated white mice intracerebrally, intravenously, intraperitoneally, intratracheally and subcutaneously, they were unable to produce involvement of the central nervous system without visceral involvement, chiefly of lung and kidney and less frequently of liver and spleen. Intranasal inoculation caused a severe rhinitis and sinusitis. Organisms spread out beneath the mucous membrane and beneath the cribriform plate but did not invade the nervous system.

REPORT OF CASES

CASE 1.—J. A. C., a 31 year old white man, was admitted to the medical service of the Robert Long Hospital on April 16, 1933, complaining of severe and persistent headaches of six weeks' duration. The headaches were accompanied with nausea. During this interval he had become increasingly nervous and

6. Wade, L. J., and Stevenson, L. D.: Torula Infection, Yale J. Biol. & Med **13**:467-476 (March) 1941.

reckless, until he was forced to quit working. On April 10, 1933, he had had a generalized convulsion. The past history was irrelevant except for partial deafness in the left ear for twenty years. Five years before the patient's admission this ear had drained for a short time.

General physical examination revealed nothing remarkable. Neurologic examination showed a semistuporous patient who could respond at times but was disoriented as to time and place. Initially the cranial nerves were all intact except for slight blurring of the left disk. Later, definite papilledema developed on the left and the tongue protruded to the left. Nuchal rigidity and positive Kernig's sign were present. Right abdominal, patellar and achilles tendon reflexes were diminished. There was considerable weakness in the muscles on the right.

Urinalysis indicated nothing abnormal. There was slight anemia. Counts of white blood cells ranged from 4,500 to 12,000 with a shift to the left. The pressure of the spinal fluid was constantly elevated; cell counts initially were from 280 to 300, later dropped to 100, with a predominance of polymorphonuclear cells; Pandy's test showed globulin (from 3 plus to 4 plus); sugar was too low to be read on the colorimeter. Yeast cells considered to be Torula histolytica were present.

The patient's course in the hospital was progressively downhill. Attacks of vomiting were frequent, and hiccuping was often troublesome. Repeated spinal punctures were made in an effort to relieve his distress. On April 27, 1933, a left temporal decompression was performed. On May 5, 1933, a left simple mastoidectomy was done. His temperature ranged from normal in the morning to 101 F. in the evening. Death occurred on June 22, 1933, fifty-two days after the patient's admission to the hospital.

An autopsy was performed one hour post mortem. Grossly the meninges appeared hyperemic, with many small grayish masses in the arachnoid and just beneath it. The brain was hyperemic, and there was a soft fluctuant mass in the anterior portion of the left frontal lobe; the lateral ventricles seemed enlarged, and their interior was filled with a mossy substance which later proved microscopically to be yeastlike fungi. An abscess 1 cm. in diameter, full of thick, green pus, was found in the apex of the left lung. Many gray abscesses were seen in the cortex of the kidney. Microscopic sections confirmed the presence of Torula organisms in the abscesses seen grossly. In addition, a single focal, granulomatous lesion containing yeast cells was seen in the adrenal glands.

This case is one of generalized torulosis in which focal neurologic signs predominated clinically. Samples of sputum and cultures from the left mastoid process showed no sign of the organism. The pathologist considered the lung abscess as the probable primary lesion because of the age of the scar tissue present. The duration of the illness was three and a half months.

Case 2.—E. B., a white man, aged 55, was admitted to Robert W. Long Hospital on Jan. 2, 1942, because of dysuria, ulcers on the skin, deafness and headaches. In the early summer of 1941 he began to have intermittent urinary obstruction, pyuria, dysuria and cramping pains in the lower part of the abdomen. Gross hematuria occurred on at least one occasion. In August 1942 he was admitted to Methodist Hospital in Indianapolis, and one month later a transurethral prostatectomy was performed. The tissue obtained was reported to the patient's family as indicative of carcinoma of the prostate. Ten days after discharge he was readmitted in uremic coma. By November 10 he had recovered sufficiently

to be discharged. At about this time he begun to suffer very persistent headaches, and the skin lesions were first noted. These began as a large papule with a surrounding area of erythema. In a short time the elevated portion became covered with vesicles, which were later replaced with a tenacious crust. The first lesion appeared on the neck, and others soon followed on the face, scalp, upper part of the trunk and right wrist. The headaches were limited to the temporal area and were greater on the left side. After the onset of his headaches he became deaf in the right ear, and in the middle of the following December he suddenly lost the hearing of his left ear.

General physical examination indicated nothing abnormal except for the skin lesions previously described. Neurologic examination showed the cranial nerves to be normal except for slight papilledema, considerably diminished hearing by both air and bone conduction, slight right hemiparesis, and a staggering gait.

A biopsy of one of the skin lesions showed a microscopic picture which was considered consistent with the diagnosis of histoplasmosis of Darling. Urinalyses showed the specific gravity to vary from 1.004 to 1.012, with a faint trace of albumin, pus cells and many red cells. Hemograms showed a slight anemia and white cell counts up to 11,800 with a shift to the left. Pressure of the spinal fluid was 85 mm. of water. Examination of the spinal fluid revealed 31 cells, globulin 3 plus by the Pandy test, sugar 23 mg. per hundred cubic centimeters, protein 250 mg. per hundred cubic centimeters and yeast cells. Blood cultures and specimens of sputum also contained yeast cells. Roentgenologic examination of the chest showed accentuation of the lung markings in both hilar areas with no definite consolidation.

The patient's course was ingravescent, with death occurring on March 21, 1942. The final clinical diagnosis was histoplasmosis.

Postmortem examination performed three hours after death showed grossly the skin lesion previously described; large, white, granulomatous lesions in the right lung, the largest of which measured from 2 to 4 cm.; an annular nodule around the left ureter; numerous small white nodules in both kidneys, and enlarged mesenteric lymph nodes containing white material similar to that described in other tissues. Microscopic examination revealed small spherical yeastlike fungi in the lungs, kidneys, adrenal glands, skin, prostate, urinary bladder, mesenteric lymph nodes and meninges. The cultural characteristics of these organisms fulfilled the criteria for Torula histolytica. No evidence of prostatic carcinoma was found.

COMMENT

This case of systemic torulosis is unusual in that visceral symptoms were dominant and in that the involvement of the central nervous system was slight. The diagnosis through biopsy of histoplasmosis of Darling undoubtedly confused the clinical picture, and the paucity of gross evidence of involvement of the brain probably was responsible for the pathologists' not obtaining more detailed studies in an attempt to explain the neurologic findings. While involvement of the kidney is frequent, both clinically and experimentally, this is probably the first case in which genitourinary involvement was the presenting symptom. The previous diagnosis of carcinoma of the prostate is difficult to evaluate in view of the serious abnormalities discovered in the lower

urinary tract at autopsy. Duration of the disease was approximately ten months.

CASE 3.—E. G., a 42 year old white man, was admitted to Robert W. Long Hospital Oct. 25, 1944. · Six weeks previously he had begun to have very severe generalized headaches, which soon were accompanied with nausea and vomiting. For five weeks photophobia and diplopia had been present. A staggering gait and stiffness of the neck had been noted for approximately one week. The patient had been employed as a molder for seventeen years. Two years previous to the onset of his present illness he had quit work because of increasing weakness, fatigue and shortness of breath. At that time a diagnosis was made of silicosis. He attempted to work at lighter jobs, beginning in February 1941, but was forced to quit in June. He had had a cough productive of tenacious, gray sputum for a number of years, and after quitting work in June, he was found to have tubercle bacilli in his sputum. Significant physical abnormalities observed on general examination were limited to the thorax. The chest was emphysematous in shape, and excursions were slightly increased on the left. Both apexes were slightly dull, and bronchial breath sounds and a few crepitant rales were heard in the left apex. Neurologic examination showed moderate opisthotonus, nuchal rigidity, choked disks (·2 D.), left ophthalmoplegia, a negative Romberg sign and staggering, apparently because of weakness.

Urinalyses were within normal values. Hemograms showed normal red blood cell elements, and the highest white blood cell count was 10,100, with a shift to the left in the differential counts. Spinal fluid pressure was 300 mm. of water, cell counts from 8 to 10, sugar 49 mg. per hundred cubic centimeters initially and too low to be read terminally, protein 139 mg. per hundred cubic centimeters and yeast cells in all specimens. Urine and blood cultures both were positive for yeast cells. All of these cultures were proved to be Torula histolytica. Specimens of sputum were repeatedly positive for acid-fact bacilli. Roentgenologic examination of the chest revealed conditions considered to be indicative of advanced silicotuberculosis.

Treatment consisted of saturated solution of potassium iodide, 11 drops (11 grains [0.715 Gm.]) three times a day and sulfadiazine in doses adequate to maintain a level in the blood of approximately 10 mg. per hundred cubic centimeters. The patient's course was downhill, characterized by almost intractable headaches and persistent vomiting. Neurologic conditions observed remained unchanged. Death occurred on November 18.

Autopsy performed four and a half hours post mortem revealed numerous gray, shotty, calcified nodules throughout both lungs, adhesions binding both lungs to the wall of the chest and a cavity some 10 cm. in diameter in the left apex; the meninges appeared thickened and opaque. Microscopic examinations showed silicotuberculosis and yeast cells in the lungs, yeast cells in the spleen and tuberculous splenitis, yeast cells in the glomeruli of the kidneys, yeast cell granulations in the adrenal glands, perivascular yeast cell granulations throughout the brain and a yeast cell meningitis.

<center>COMMENT</center>

While the silicotuberculosis in this patient was sufficiently extensive to be ultimately fatal, we believe that his case may justifiably be classified as another case of generalized torulosis. Sulfadiazine and iodides were given without avail in an effort to alter the course of

his disease. The ten week course is characteristic of the fulminating form of the disease.

CASE 4.—C. S., aged 44, has been admitted six times ·to Indiana University Medical Center. The first of these was in November 1943. The onset of his illness was in February 1938, when he had progressively increasing occipital headaches, which later also involved the frontal area. He was treated for sinusitis, but with the onset of fever in April 1938 a diagnosis of meningitis was made, and he was hospitalized for three weeks. During this period diplopia and deafness of the right ear developed. After he returned home he continued to suffer from headache and backache, and his family noted some personality changes.

Because of his failure to improve he was referred by his local physician, Dr. G. F. Schmidt, to Mayo Clinic in August 1938. Neurologic examination by Dr. F. A. Carmichael revealed "anosmia, bilateral, and an increase in the tendon reflexes, slightly more so on the right side throughout. The abdominal reflexes also were present, and there were no signs referable to the pyramidal tract in either the upper or the lower extremities. There was a distinct tremor of the arms and legs bilaterally. There was no cervical rigidity or tenderness to percussion over the head or spine. No bruits were audible, but there was slight tenderness to palpation in the left posterolateral cervical region." To exclude the possibility of an intracranial mass an encephalogram was made. "There was an abnormal amount of air in the subarachnoid spaces with a secondary dilatation of the ventricular system without shift. The picture was that of an extensive degenerative lesion." The spinal fluid was yellow in color, the reaction to the Wassermann test negative, the total protein 80 mg. per hundred cubic centimeters, the Nonne reaction positive, the cell count 175 and the colloidal gold curve 5553210000. No cultures were made. Serologic reactions of the blood were Kline 3 plus, Kahn negative and Kolmer negative. "A roentgenogram of the chest revealed scattered miliary calcification, probably of no significance; other conditions were normal. The sinuses of the head and the sella turcica were normal on roentgenologic examination." Because of the history of a positive reaction to the Wassermann test and of treatment for syphilis in the past, further therapeutic tests were advised. In January 1939 his home physician stated that he had shown definite improvement but was still moody and nervous.[7]

The patient was ultimately able to return to work on a farm, but by April 1943 he was experiencing so˙much difficulty in walking and so much pain in his back that he was forced to stop working. His diplopia had receded soon after his initial attack of meningitis, but the deafness had persisted. He had gradually acquired a staggering gait, and he now experienced difficulty in stopping or turning after he had walked a short distance. He also had difficulty in expressing himself. There was no difficulty in pronunciation, but rather one of choosing the right word.

Physical examination on his first admission, on Nov. 25, 1943, revealed nothing remarkable except with respect to the nervous system. The left pupil was larger than the right, and both reacted to light and showed accommodation. No constriction of the visual fields was present. A slight pallor in both optic disks was observed. Air conduction of sound was absent, and bone conduction was less in the right ear. The ear drum was normal. There was a coarse tremor of the tongue, which deviated to the left. The palate and the uvula deviated to the right. There was hemiparesis of the right side, including the face. Reflexes of the tendons were active and equal. No pathologic reflexes were present.

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7. Montgomery, H.: Personal communication to the authors.

Sensory examination revealed nothing abnormal. Slight ataxia was shown by the reaction to the finger to nose test. There was a negative Romberg sign. A coarse tremor of the intention type was present in the upper extremities. The patient's gait was propulsive; he experienced difficulty in stopping and turning and a tendency to veer to the right on walking with the eyes closed. The sensorium was clear, but the patient was suspicious and surly in nature.

On laboratory examinations, a urinalysis and a hemogram showed nothing abnormal. Serologic reactions of the blood were negative. The pressure of the spinal fluid was 230 mm. of water. The white cell count was 122, with 5 polymorphonuclear cells and 95 per cent lymphocytes. Pandy's test showed globulin 4 plus; sugar was too low to be read on the colorimeter; there were 268 mg. of protein per hundred cubic centimeters; reaction to the Wassermann test was negative, and there was a gold curve of 5555553310. After seven days' incubation, yeast cells were observed which, after further examination, were considered to be Torula histolytica.

Roentgenologic examination showed the chest to be normal except for numerous calcified parenchymatous deposits, measuring from 1 to 3 mm. in diameter, scattered throughout both lung fields. Roentgenograms of the skull and the mastoid processes were considered to show nothing abnormal.

Before additional examinations could be made the patient became very dissatisfied and signed his own release from the hospital.

The patient was persuaded to return to the hospital for further study on Feb. 21, 1944. On reexamination at that time, the patient's condition was found to be unchanged. Torula organisms were found in urine cultures but were absent in repeated sputum, blood and stool cultures. Cultures from washings of the maxillary sinuses also were negative. The spinal fluid remained the same except for some increase in the total protein. Roentgenologic examinations of the accessory nasal sinuses revealed considerable thickening of the lining membrane of the left antrum and some clouding of the frontal sinuses, particularly on the right. The ethmoid cells, sphenoid sinus and right antrum appeared relatively free from pathologic conditions. Complete gastrointestinal roentgenograms, taken after a barium sulfate meal and a barium sulfate enema, showed stomach and intestines to be normal. Examination of the urinary tract by excretory urography revealed normal kidneys, ureters and bladder.

On March 9, 1944, the patient was placed on sulfadiazine therapy and a level in the blood of 8 to 14 mg. of sulfadiazine per hundred cubic centimeters was maintained until his discharge on April 11, 1944. At the time of discharge he seemed considerably improved. His hemiparesis was almost gone, the ataxia less noticeable and his gait more certain. Subjectively, his headaches were less and he was more cheerful. The last examination of the spinal fluid, made the day before discharge, revealed that the fluid still was positive for Torula organisms, however.

He was seen as an outpatient on May 11, 1944, and, because of a recurrence of symptoms, was placed on a six week course of sulfadiazine therapy under the supervision of his local physician, Dr. Irvin H. Scott, of Sullivan, Ind. While under this therapy the patient ceased to have headaches, but his backache persisted and he still had difficulty in walking, especially at night.

He was readmitted to the hospital on June 26, 1944, and given 15,000 units of penicillin intramuscularly every three hours from June 27 to July 7. Penicillin was given intrathecally in doses of 20,000 units on June 27 and 29 and July 1. No Torula organism was found in the spinal fluid withdrawn before each intrathecal injection, but otherwise *the spinal fluid remained unchanged*.

He was again admitted to the hospital on Sept. 11, 1944, for reexamination. At that time he stated that he suffered little from backache and that his walking had continued to improve. Neurologic examination now showed nothing abnormal except for deafness in the right ear, slight ataxia on the finger to nose test, and a tendency to veer to the right while walking. Spinal fluid culture was negative for Torula, but the cell count was 128 with 99 per cent lymphocytes, Pandy's test indicated globulin (4 plus), and sugar was too low to be read.

When seen as an outpatient on Nov. 9, 1944, the patient had resumed light work about the house and had no subjective complaints. He was given saturated solution of potassium iodide and instructed to take 30 drops three times a day, increasing the dose by 1 drop a day until he was taking 50 drops three times a day.

He continued to do well until February 1945, when he began to notice increasing difficulty in walking and a tendency to propulsion. Because of the recurrence of symptoms he was readmitted to the hospital on March 19, 1945. Spinal fluid culture of March 22 was positive for Torula organisms. Treatment consisted of intramuscular doses of 20,000 units of penicillin every four hours from March 19 to April 4 and intrathecal doses on March 21 and 27 and April 4. This was followed by sulfadiazine from April 5 to April 15. The spinal fluid still contained Torula organisms on March 21, but none was present after two weeks' incubation in a specimen obtained March 26.

When seen on May 19, 1945, after the course of penicillin and sulfadiazine, he was feeling better and had gained in weight. A slightly staggering gait and the tendency to veer to the right while walking were again noted. Left temporal and right occipital headaches still were present. There was some general weakness of motor power and a coarse tremor of the hands. Spinal fluid culture still was positive for Torula histolytica.

COMMENT

It may be stated definitely that this patient is suffering from meningoencephalitis and a probable renal infection, inasmuch as Torula organisms were isolated from the urine. His initial improvement after the use of sulfadiazine was striking, but on subsequent courses of that drug he has failed to show similar gain. The lack of response to intrathecal and intramuscular doses of penicillin is comparable to the experience of Harford and his colleagues.[8] The duration of illness of seven years is the second longest recorded case in the literature, and though his spinal fluid still was positive at his last visit to the clinic, there has been no gross change in his condition in the past year.

SURVEY OF THE CURRENT LITERATURE

The 7 cases in the current literature in the table in which the duration is considered unknown deserve further comment, since these concern patients still living at the time of publication of their reports. The most important of these is case 4 of Reeves, Butt and Hammack.[9] The known duration of this 21 year old woman's illness is at

8. Harford, C. G.: Martin, S. P.; Hagemann, P. O., and Wood, W. B.: Treatment of Staphylococcic, Pneumococcic, and Other Infections with Penicillin, J. A. M. A. **127**:325-329 (Feb. 10) 1945.

9. Reeves, D. L.: Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and the Central Nervous System, Arch. Int. Med. **68**:57-79 (July) 1941.

least seven years and eight months, the longest on record. She is suffering from involvement of the central nervous system plus a pulmonary lesion with a draining sinus through the wall of the

Summary of Cases According to the Schema of Levin [3]

Sex of patient:	Levin	Binford 1940	Beck-Voyles 1945	Total
Male...	39	9*	23	71
Female.......................................	20	4*	13*	37
Age distribution in years:				
Under 10.....................................	1	2	1	4
10-19...	6	1	4	11
20-29...	9	3*	9	21
30-39...	9	3	8	20
40-49...	15	1	4	20
50-59...	16	1	7	24
60-69...	2	2	2	6
Not stated...................................	2	0	0	2
Duration of illness in months:				
0-1...	3	3	3	9
1...	6	0	1	7
2...	10	3	6	19
3...	9	1	5	15
4...	8	0	5	13
5...	3	1	2	6
6...	3	2	1	6
7...	1	0	1	2
8...	2	0	0	2
9...	1	0	1	2
10-12...	1	0	1	2
13-24...	3	0	1	4
25-36...	5	0	1	6
37-48...	0	1	1*	2
49-60...	0	1	0	1
61-72...	1	0	0	1
Unknown.......................................	4	0*	7	11
Organs involved including the central nervous system:				
Lungs..	9	4	7	20
Generalized..................................	8	1	6	15
Kidney.......................................	2	2	8	12
Spleen.......................................	1	1	3	5
Adrenal glands...............................	1	1	5	7
Abdominal nodes..............................	1	0	3	4
Peribronchial nodes..........................	1	0	1	2
Tonsil.......................................	3	0	0	3
Subcutaneous tissue..........................	2	0	2	4
Skin...	5	0	1	6
Central nervous system only..................	30	4*	20	54
When diagnosed:				
Post mortem..................................	23	8	6	37
Ante mortem..................................	37	5*	29*	71
How diagnosed:				
Antemortem cultures only.....................	10	4*	26*	40
Biopsy of the brain ante mortem.............	2	1	5	8
Postmortem histologic sections..............	22	0	4	26
Cultures and postmorten histologic sections.....	26	0	1	27

* These cases appeared in Binford's review, but were advanced to the next column in duplicate with correction in number.

chest. When last seen by Dr. Hammack [10] in December 1944, she still was having difficulty in walking and with her vision. Her spinal fluid contained no Torula organisms on culture, but the cell count was

10. Reeves, D. L.: Butt, E. M., and Hammack, R. W.: Personal communication to the authors.

29 and the protein 200 mg. per hundred cubic centimeters. She has received iodides to the limit of her tolerance from time to time and the Torula antigen prepared by Dr. Kreuger of the University of California (Berkeley) more or less continuously.

The case of the 9 year old girl reported by Marshall and Teed [11] is another instance in which a person suffering with Torula meningitis is known to be living at the present time. Although Dr. Teed is now unavailable, being overseas as a commander in the United States Navy, an inquiry concerning this child was answered by his wife.[12] She states that the child "is living, in school, active and well, save for occasional headaches." The onset of her illness was in December 1941. She was treated with mastoidectomy and repeated courses of sulfadiazine. She had been unable to attend school and apparently had been considered of subnormal intelligence before her treatment. This may have been due to her deafness; nevertheless, since her treatment she has been able to resume a relatively normal life four years and four months since the onset of her symptoms.

Case 3 of Burger and Morton [13] does not properly belong in a review of systemic Torula infection since the infection was limited to the tissues of the thigh. It is included, however, for the sake of completeness in the review of the literature. This patient was treated by disarticulation of the femur and there has been no recurrence. Case 5 necessitated revision of Binford's review, since it is a follow-up of Magruder's case 3.[14] This case is that of a 22 year old Negress who died at her home after an illness of three years and four months.

Our own case 4 is one of those in which the duration of the illness is considered unknown. Follow-ups were not obtained on the remaining 3 cases. Dr. E. C. Toone,[15] who reported the case of an 18 year old Negress, is now overseas as a major in the United States Army. This patient was seen during the acute phase of her illness in March 1938. When last seen, in September 1940, her spinal fluid still contained Torula histolytica. Major Toone [16] referred us to her family

11. Marshall, M., and Teed, R. W.: Torula Histolytica Meningoencephalitis: Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy; Preliminary Report, J. A. M. A. **120**:527-529 (Oct. 17) 1942.

12. Marshall, M., and Teed, R. W.: Personal communication to the authors.

13. Burger, R. E., and Morton, C. B.: Torula Infection: A Review and Report of Four Cases, Surgery **15**:312-325 (Feb.) 1944.

14. Magruder, R. G.: Report of Three Cases of Torula Infection of the Central Nervous System, J. Lab. & Clin. Med. **24**:495-499 (Feb.) 1939.

15. Toone, E. C., Jr.: Torula Histolytica (Blastomycoides.Histolytica) Meningitis: Report of a Case with Recovery, Virginia M. Monthly **68** : 405-407 (July) 1941.

16. Toone, E. C.: Personal communication to the authors.

physician for information concerning her later course, but we have received no reply from him in response to our inquiries.

The remaining 2 cases are those of a 27 year old man reported by Farrer [17] and a 32 year old man reported by Dickmann, Veppo and Negri.[18] Farrer's patient was convalescent from the acute phase of his illness at the time of reporting, but he still had symptoms. The symptoms of the patient reported by Dickmann and his colleagues had been present since September 1941. On Feb. 2, 1942, an occipital craniotomy disclosed a tumor on the left cerebellar hemisphere. Torula organisms were found in his spinal fluid on February 26 and were identified in the tumor mass removed by operation. He was released against the advice of the surgical staff on March 4, 1942.

SUMMARY

1. A summary of the literature, including all reported cases from Binford's review [4] in 1940 to the present date, has been presented according to Levin's schema.[3]

2. The pertinent clinical and laboratory observations have been emphasized.

3. It is suggested that the course of infection may be fulminating or chronic and that if the patient survives the initial acute phase, the duration of illness may be two to three years.

4. The pathogenesis remains unexplained.

5. Four additional cases with observations at autopsy have been presented.

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17. Farrer, R.: Torula Meningitis, Roy. Melbourne Hosp. Clin. Rep. **12**:31-32 (Dec.) 1941.

18. Dickmann, G. H.; Veppo, A. A., and Negri, T.: Torulopsis del sistema nervioso central (cerebelo) de fornea tumoral, Rev. neurol. de Buenos Aires **7**: 347-360 (Oct.-Dec.) 1942.

SYSTEMIC INFECTION DUE TO TORULA HISTOLYTICA (CRYPTOCOCCUS HOMINIS)

II. Effect of Chemotherapeutic Agents in Experimentally Produced Infections

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BECAUSE of the apparent improvement following treatment with sulfadiazine observed in the case reported by Marshall and Teed and in our own case 4 my colleague and I determined to test the efficacy of this substance in experimentally produced infections with Torula organisms. Since iodides have been a time-honored remedy in fungus infections on what seems to be a purely empiric basis, it was thought that they also should be subjected to experimental evaluation.

PROCEDURE

Four species of animals were used, rats, rabbits, guinea pigs and dogs. All species were inoculated at the same time with emulsions of Torula histolytica originally obtained from the spinal fluid culture of case 4. These organisms had been subcultured on Sabouraud's dextrose agar and were suspended in sterile isotonic solution of sodium chloride before injection. The number of organisms injected was standardized by a preliminary enumeration of organisms per cubic millimeter in a standard blood-counting chamber. The emulsion was diluted and the organisms counted in the same manner as are red blood cells. The number of organisms injected in each species is indicated in the table. Dogs and rabbits were given intraveneous injections; guinea pigs, intracardial and rats, intraperitoneal.

Each species was divided into four groups designated as the control, iodide, sulfadiazine and sulfadiazine and iodide sections. After a period of about two weeks, when the animals began to appear ill, treatment was started with the drugs indicated by their section. The drugs were dissolved in the drinking water and placed in the cages for the animals. Potassium iodide was supplied in the amount of 6 Gm. per liter, and sulfadiazine 4 Gm. per liter. The dose of iodides would correspond to 1 grain per pound (243 mg. per kilogram), which is the usual dose per day for a man in fungus infections. Levels of sulfadiazine in the blood were obtained at weekly intervals and were

maintained between 12 and 18 mg. per hundred cubic centimeters. When the animal took insufficient sulfadiazine in the drinking water an additional amount was given in tablet form to maintain this level.

Fig. 1.—Photomicrograph of rat lung showing almost total loss of normal structure and total infiltration with Torula organisms without exudative phenomena and with little fibrosis (× approximately 250).

Determinations of sulfadiazine levels were made by an adaptation of the method of Bratton and Marshall[1] devised by Dr. T. Makovsky

1. Bratton, C. A., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:437 (May) 1939.

of the Department of Clinical Pathology of the Indiana University Medical Center. This is truly a micromethod, requiring only 20 cc. of blood for the determination. The reagents required are 12 per cent trichloroacetic acid, 0.1 per cent sodium nitrite, 0.5 per cent ammonium sulfamate, and 0.1 per cent ethylenediamine.

PROCEDURE

1. Draw up 20 cu. mm. of blood into a micropipet.

2. Discharge in 1 cc. of distilled water in a Wassermann tube. Agitate the blood and rinse the pipet by drawing the fluid up and discharging it several times.
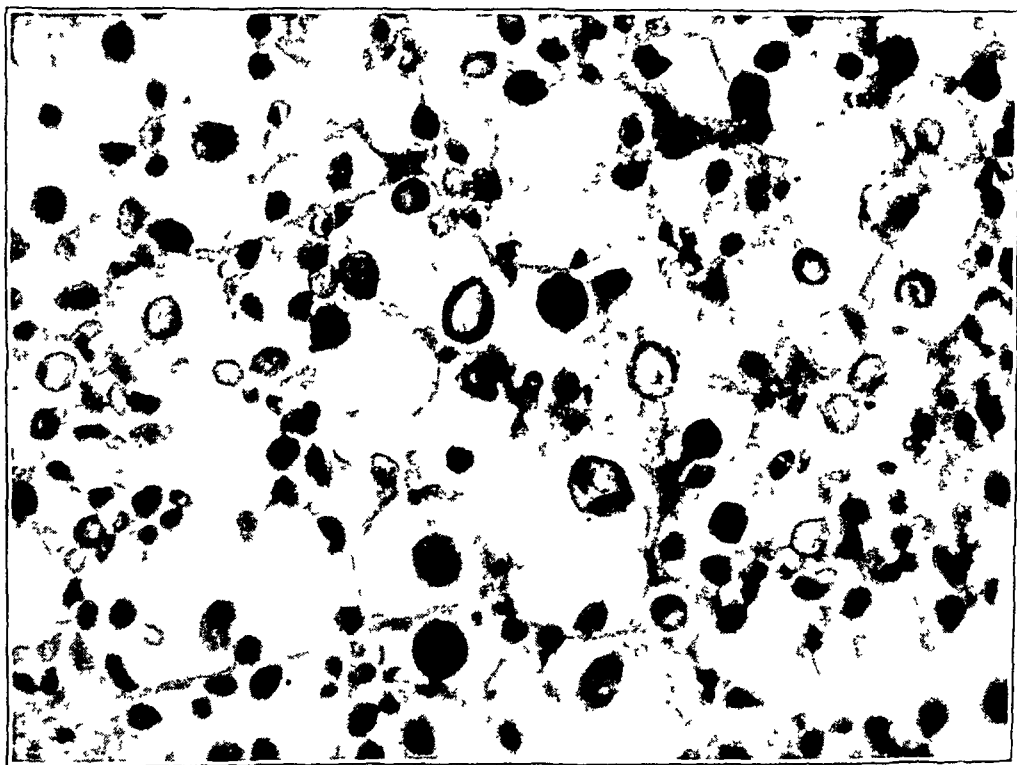
Fig. 2.—Lung section showing the morphology of Torula histolytica·(× 800).

3. Allow hemolysis for about one minute.

4. Precipitate the protein by adding 0.6 cc. of 12 per cent trichloroacetic acid. Mix and allow to stand for three minutes

5. Centrifuge at high speed for four minutes to pack the precipitate well.

6. Pipet off 1 cc. of the supernatant fluid with a volumetric pipet   Discharge this into a Wassermann tube.

7. Add 0.1 cc. of 0.1 per cent sodium nitrite, mix well by shaking; let stand three minutes.

8. Add 0.1 cc of 0.5 per cent ammonium sulfamate, mix well by shaking and let stand two minutes.

9. Add 0.1 cc. of 0.1 per cent ethylenediamine; mix well; let stand two minutes.

10. Compare with a standard in a microcolorimeter.

A standard containing 20 mg. of sulfadiazine per hundred cubic centimeters is treated in exactly the same manner as the unknown.

On the death of the animal and at the conclusion of the experiment a postmortem examination was performed immediately and representa-

Fig. 3.—Photomicrograph of dog brain showing an area of meningitis. There are few exudative phenomena and little phagocytosis or fibrosis (× 200).

tive sections were taken for microscopic examination. Sections were stained with eosin-hematoxylin and by Gram-Weigert methods.

RESULTS

Results of these experiments are presented in the table. This table is so arranged that opposite each species of animal is stated the

number of organisms with which the animal was inoculated and the day on which treatment was begun. The numbers beneath each group indicate the duration of life after inoculation, and "present" or "absent" indicates the presence or absence of Torula histolytica in microsections obtained from postmortem examination of the animals.

The Effect of Potassium Iodide, Sulfadiazine and Sulfadiazine and Potassium Iodide on Torula Organisms

Dog; Inoculum—Fifteen Million Organisms. Treatment Started Fifteenth Day After Inoculation

Control		Potassium Iodide		Sulfadiazine		Sulfadiazine and Potassium Iodide	
18	Present	23	Present	39	Present	34	Absent
71	Absent *	24	Absent	24	Present	34	Present
71	Present *	78	Present	82	Absent *	39	Absent
71	Absent *	82	Absent *	39	Present	40	Present

Rabbits; Inoculum—Seven Million Organisms. Treatment Started on Twelfth Day After Inoculation

Control		Potassium Iodide		Sulfadiazine		Sulfadiazine and Potassium Iodide	
23	Present	27	Present	29	Present	24	Present
73	Present *	44	Absent	79	Absent *	29	Present
73	Absent *	73	Present *	79	Absent *	37	Absent
79	Absent *	79	Present *	79	Absent *	83	Absent *
		79	Present *	79	Absent *	83	Absent *
				79	Present *		

Guinea Pigs; Inoculum—Three Million Organisms. Treatment Started on Eleventh Day After Inoculation

Control		Potassium Iodide		Sulfadiazine		Sulfadiazine and Potassium Iodide	
5	Absent	14	Present	18	Present	14	Present
9	Absent	15	Present	26	Present	24	Present
10	Absent	22	Absent	32	Present	50	Present
23	Absent	23	Absent	35	Present	53	Present
24	Present †	38	Present	36	Present	58	Present
31	Present	47	Present	38	No slides †	63	Present *
32	Present	49	Present	44	Present	63	Present *
33	Absent	52	Present	46	Present	63	Present *
34	Absent	61	Present	48	Present	63	Absent *
				63	Present		

Rats; Inoculum—Two Million Organisms. Treatment Started on Thirteenth Day After Inoculation

Control		Potassium Iodide		Sulfadiazine		Sulfadiazine and Potassium Iodide	
28½	Present	20	Present	35	Present	20	Present
36	Present	33	Present	51	Present	32	Absent
50	Present	36	Present	56	Present	33	Present
56	Present	40	Present	57	Present.	39	Present
86	Absent *	43	Present	64	Present	56	Present
86	Absent *	46	Present	65	Present	61	Present
86	Absent *	46	Present	69	Present	64	Present
86	Present *	64	Present	77	Present	69	Present
86	Present *	69	Absent	81	Present	75	Present
86	Present *	70	Present	86	Present *	86	Present *
86	Absent *	86	Present *	86	Absent *	86	Present *
		86	Present *				

* Killed.
† No microsections.

COMMENT

Reference to the table quickly indicates that the drugs given had no beneficial effects with respect to the morbidity and the mortality among the experimentally infected animals. In fact, many of the control animals had a better course and less evidence of infection at the time of death than the treated groups. My colleague and I do not feel that this
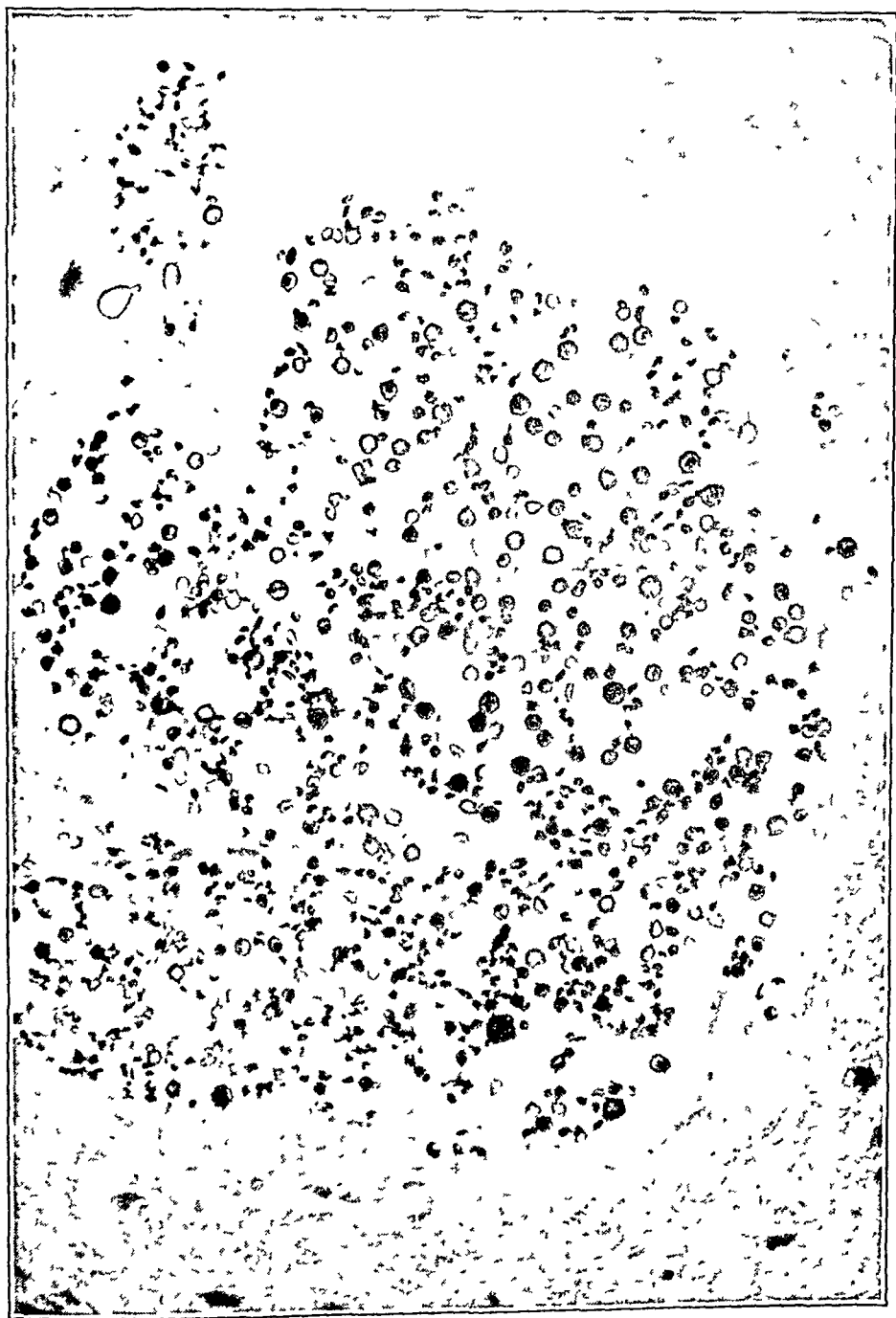
Fig. 4.—Photomicrograph of dog brain showing a small focal lesion not associated with the vascular system. Here may be noted budding Torula organisms, phagocytosis and the apparent disintegration of the cortical substance either because of lysis or because of spreading of the cortical substance by substances produced by the organism ($\times$ approximately 250).

difference is due to any deleterious effects of the drugs used. In the animals treated with sulfadiazine, anuria did not occur, and there was no microscopic evidence of renal damage of the type associated with the presence of sulfonamide toxicity. In the more susceptible animals
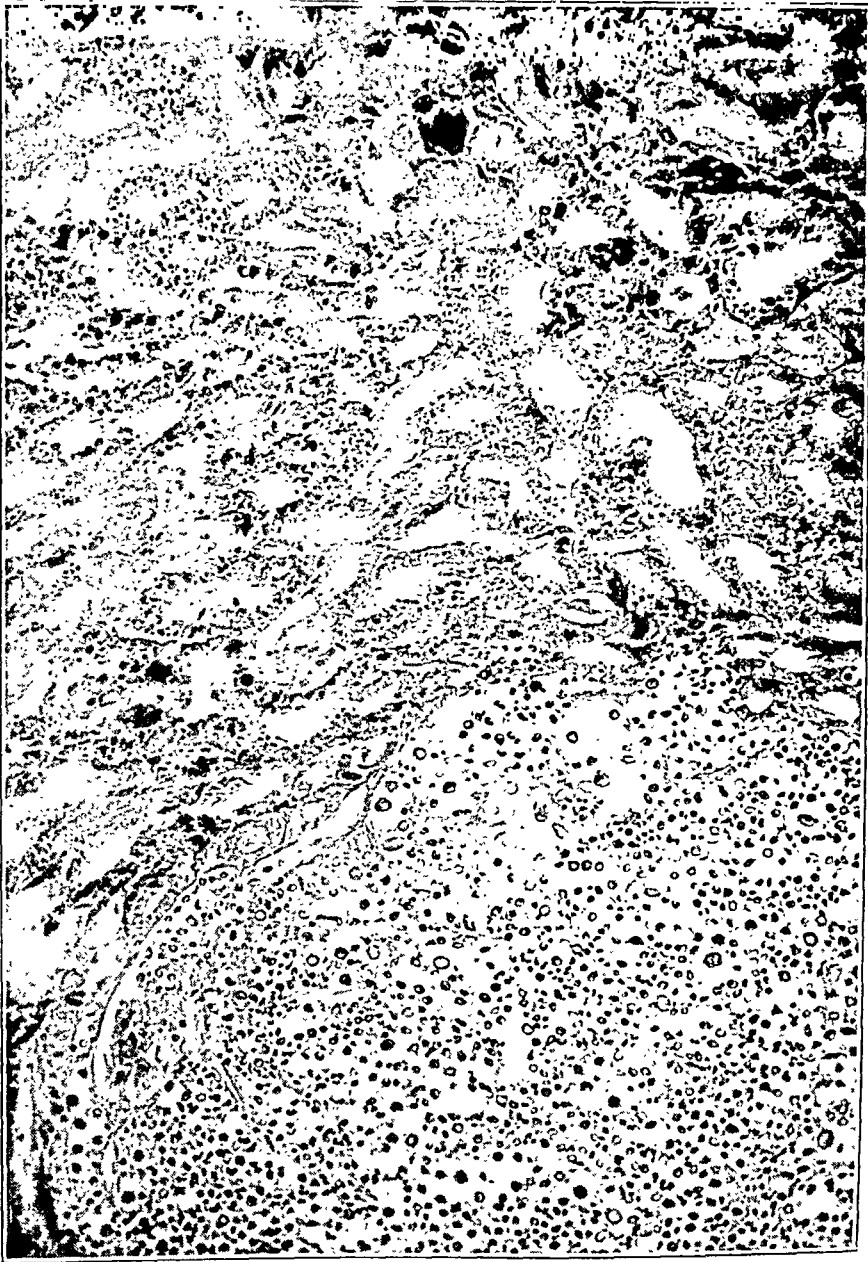
Fig. 5.—Photomicrograph showing a well localized lesion of the renal cortex (× approximately 250).

the mortality rate was actually higher because of infection with Torula organisms, and fewer animals had to be killed at the termination of the experiment in the treated groups. The only exception to this was the

guinea pig section treated with both sulfadiazine and iodides. This might give rise to some speculation as to the undesirable effects of the drugs used on the course of the infection, even though the dose was a subtoxic one.
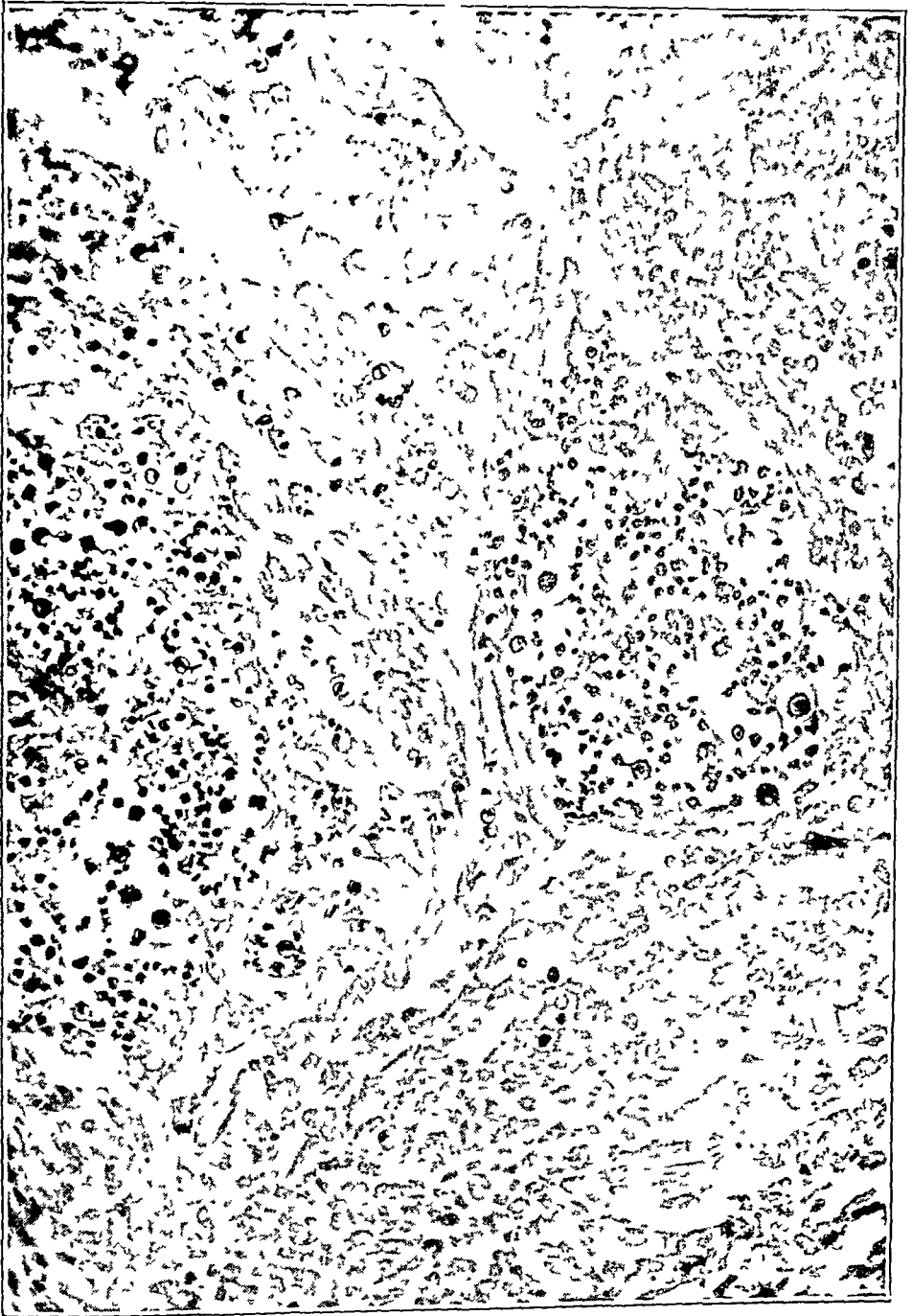
Fig. 6.—Photomicrograph of the spleen of a guinea pig demonstrating Torula lesions ($\times$ approximately 250).

It might appear that the inoculum was not great enough in less susceptible animals, since many of them had to be killed to terminate

the experiment or had no microscopic evidence of infection with Torula organisms.

It was not our aim to produce immediate death, but rather a subacute infection similar to that clinically seen. Jones and Klinck[2] recently reported a similar study of the effects of sulfadiazine in experimental infection of mice with Torula organisms. Their results coincided with our own in that there was no difference between the treated and the control groups. They also tested the effects of penicillin, and again there was no difference between the control and the treated groups. Their experiment differs from ours in being more acute in type, the inoculant being adjusted to produce death in twelve and a half days.

Penicillin was not used as a treatment because it was not available in sufficient quantity at the time these experiments were conducted. Neither was the injection of killed organisms or other Torula antigens tested since we feel this already had been adequately investigated by Stoddard and Cutler[3] and more recently by Hoff.[4]

In comparing the pathologic aspects of the lesions of those animals treated with potassium iodide, sulfadiazine and potassium iodide and sulfadiazine with those of the lesions of the animals in the control groups, it was impossible to find any evidence that the drugs used altered the reaction of the body to the organism. Reaction of the tissue with the exception of that of the central nervous system, was confined to a defensive fibrosis with few or no exudative phenomena. The reaction was granulomatous in nature, characterized by the formation of nodules of various sizes composed of fibrous tissue whorls with or without caseation necrosis- or hyaline degeneration, epithelioid cells, infiltration of small, round cells occasional giant cells and Torula organisms. Lesions of this type were seen in the lungs, spleen and kidneys, and to a lesser extent in the liver, heart and peritoneum. In the lung a lesion not previously described also was seen. The parenchyma of the lung was totally destroyed, and fibrous tissue encasing myriads of Torula organisms was all that remained.

In the central nervous system the reaction had a different aspect. The Torula organisms seemed to lie in small lacunas. Grossly these spaces were filled with a mucinous substance, possibly a part of the end products of parastic growth, as suggested by Reeves, Butt and

2. Jones, S. H., and Klinck, G. H.: Torula Histolytica (Cryptococcus Hominis) Meningitis: Case Report and Therapeutic Experiments, Ann. Int. Med. **22**:736 (May) 1945.

3. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, Jan. 31, 1916.

4. Hoff, C. L.: Torula Studies of Cryptococcus Hominis in Mice, J. Lab. & Clin. Med. **27**:751 (March) 1942.

Hammack.[5] The infection of the brain and spinal cord was a generalized one involving the deep brain substance, the perivascular spaces and the meningeal coverings of these organs. Any one or all of these lesions may appear simultaneously, which would substantiate the criticism of Freeman's classification [6] by Longmire and Goodwin.[7] The lesions may represent the lytic process, as suggested by Stoddard and Cutler, or the spreading of the brain substance by a mucinous material, as suggested by Reeves, Butt and Hammack.[5] Glial reaction was not remarkable about the lesions in the brain substance. In the meninges the process may be localized or generalized. There was an increase in fibrous tissue with a tendency to the formation of granulomatous tissue accompanied with an infiltration of small round cells. The vascular system of the meninges was congested in nearly all cases. Giant cells, so often reported, were very seldom seen and did not seem to be a prominent part of the pathologic picture.

SUMMARY

1. Experimental studies were conducted on animals infected with Torula histolytica and treated with potassium iodide and sulfadiazine and a combination of the two drugs.

2. The results of this experiment did not indicate any beneficial effect exerted by the drug employed.

5. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and the Central Nervous System, Arch. Int. Med. 68:57 (July) 1941.

6. Freeman, W.: Torula Meningoencephalitis: Comparative Pathology in Nineteen Cases, Tr. Am. Neurol. A. 56:203, 1930.

7. Longmire, W. P., Jr., and Goodwin, F. C.: Generalized Torula Infection: Case Report and Review with Observations on Pathogenesis, Bull. Johns Hopkins Hosp. 64:22 (Jan.) 1939.

ROLE OF HISTAMINE AND ACETYLCHOLINE IN THE MECHANISM OF HEAT ALLERGY

Report of Studies on a Soldier

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INSTANCES of heat allergy, while not common, are not new. Duke[1] in 1925 grouped all hypersensitivities to cold, heat, pressure and light under the term "physical allergy." He introduced the term to indicate an altered reactivity to physical agents. It has been proposed that physical agents release a histamine-like substance in the tissues and that this, in turn, produces subsequent allergic phenomena. However, it has become increasingly apparent that histamine alone is unable to account for all these phenomena. In recent years there have been a number of investigations which tend to show that the chemical substance that mediates allergy is acetylcholine. This belief has been fostered by the fact that some allergic manifestations can be produced by certain cholinergic drugs. For example, acetylcholine chloride in doses of 30 to 40 mg. will precipitate an attack of asthma in a susceptible patient. Encouraging results have been obtained from the use of small doses of the drug in the treatment of asthmatic patients. Grant, Pearson and Comeau[2] showed by experimental evidence that the urticaria produced by emotion, exercise and warming the body was probably due to a release of acetylcholine in the skin, induced by stimulation of the efferent nerve fibers. Liberation of the H substance from the cells of the skin was, in turn, produced.

It is our purpose not to review all the literature on this complex subject but to report certain observations. Our conclusions are essentially in agreement with those of Grant and his co-workers.[2]

Recently it was our fortune to see a soldier with a characteristic physical allergy to exercise and heat. We were afforded an opportunity to study this patient and to obtain some experimental data. The results have led us to believe that the allergic phenomena of the kind observed

1. Duke, W. W.: Physical Allergy: Preliminary Report, J. A. M. A. **84**:736 (March 7) 1925.
2. Grant, R. T.; Pearson, R. S. B., and Comeau, W. J.: Observations on Urticaria Provoked by Emotion, by Exercise and by Warming the Body, Clin. Sc. **2**:253, 1936.

in this patient are based on more than one chemical substance. It was impossible to reconstruct a pure histamine allergy. Similarly, we were unable to demonstrate a pure acetylcholine reaction. The mechanism is complex, and we feel that an acetylcholine-like reaction and a histamine-like reaction are probably both responsible and act together (fig. 1). The following case report and experimental data will clarify what we mean by this concept.

REPORT OF A CASE

This patient was first seen on sick call on March 17, 1945 by one of us (G. A. P.) in an army dispensary. He presented the picture of shock. He had been inducted on March 3, 1945 and had had only one week of basic training when he was brought to the dispensary. At this time his face was flushed and
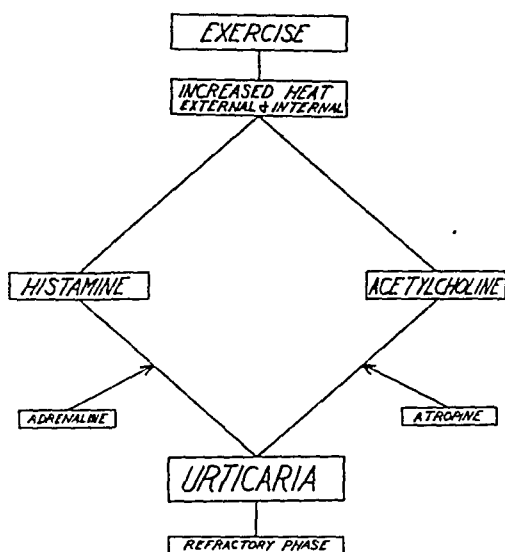
DIAGRAM ILLUSTRATING A PROPOSED
MECHANISM OF PHYSICAL ALLERGY
SEEN IN OUR PATIENT

Fig. 1.—Illustration of a proposed mechanism of physical allergy seen in our patient.

his lips were cyanotic; there was a circumoral pallor, and generally he was so weak that he had to be assisted into a chair. His temperature was 97.6 F.; his blood pressure was 80 systolic and 60 diastolic; his pulse rate was 100 per minute, and his respiration rate ranged between 20 and 25 per minute. A most striking feature was the dermatologic picture. Over his body there were numerous large wheals and a generalized urticaria. Behind his right ear there was a large edematous swelling, which was about the size of a small hen's egg. Two injections of 1:1,000 solution of epinephrine hydrochloride (0.4 cc.) fifteen minutes apart gave prompt relief, the urticaria subsiding completely in forty-five to sixty minutes.

The history of the present illness was interesting. For the past two years this patient had experienced approximately two episodes of hives a month, breaking out practically all over his body whenever he did any heavy work and became "heated." The rash consisted of wheals varying in size from that of a peanut to as large as that of a walnut. Each attack averaged one to two hours and

subsided spontaneously. There was an intense itching associated with the urticaria, starting usually in the perineal region. On being questioned, the patient stated that he believed that he perspired somewhat less than other people. He also stated that he never noticed a rash while sitting quietly in a hot room regardless of the outside temperature. It seemed that exertion was necessary for its precipitation. There was no relation of the urticaria to any particular food or drug or to contact with any known substance.

His past history was important in that he had moderately severe asthma as a child between the ages of 3 and 7 years. Even in recent years, when an infection developed in the upper part of his respiratory tract he frequently experienced a tightening sensation in his chest, but he did not refer to these
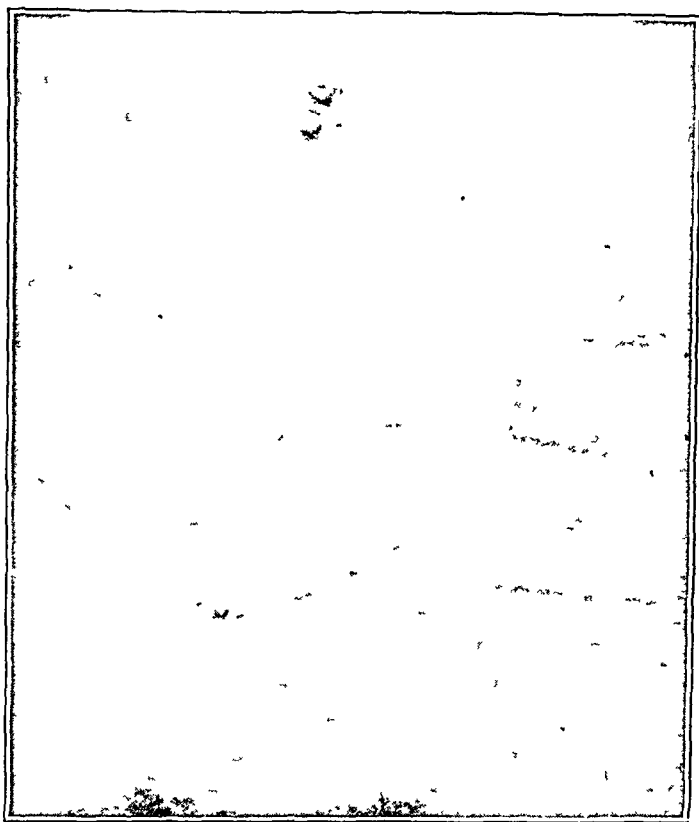
Fig. 2.—Dermographia.   (United States Army Signal Corps photograph.)

attacks as those of asthma. In his family history, both his maternal grandmother and his mother had bronchial asthma, and his mother also had an urticarial condition similar to that of her son. The patient stated that his mother had had episodes of hives following exertion for the past ten to fifteen years.

Physical examination between attacks revealed a cooperative 18 year old youth He was husky, had a ruddy complexion and bright red hair, was well proportioned and definitely did not appear to be of the apprehensive type. He was 6 feet (183 cm) tall and weighed 185 pounds (84 Kg.). His skin revealed a mild dermographia (fig. 2), but no urticaria was observed between attacks. The blood pressure was 132 mm. systolic and 78 mm. diastolic, and the pulse rate was 76 per minute. The remaining part of his examination revealed essentially normal conditions. A roentgenogram of the chest showed no abnor-

malities of the heart or lungs. The blood sedimentation rates varied from 12 to 19 mm. in one hour (normal, less than 10 mm.). The white blood cell count was 9,850, with a differential count of 48 per cent neutrophils, 38 per cent lymphocytes, 7 per cent monocytes, 3 per cent eosinophils and 4 per cent basophils. The red blood cell count was 5,440,000, and an estimation of hemoglobin revealed 18 Gm. per hundred cubic centimeters of blood. The formation of the red blood cells was normal. A white blood cell count and a differential count, which were repeated later, showed 6,850 white corpuscles, with 51 per cent neutrophils, 38 per cent lymphocytes, 1 per cent monocytes, 8 per cent eosinophils and 2 per cent basophils. The Kahn reaction of the blood was negative. The amount of calcium in the blood was 10.8 mg. per hundred cubic centimeters. A basal metabolism study on two occasions gave readings of −18 and −14 per cent. Two gastric analyses after ingestion of 7 per cent ethyl alcohol on a fasting stomach revealed no free hydrochloric acid. The fasting blood sugar content was 85 mg. per hundred cubic centimeters. A glucose tolerance test showed normal values.

CLINICAL AND EXPERIMENTAL STUDIES

1. *Effect of Physical Agents.*—(*a*) Heat: On March 31, 1945 the patient was subjected to external heat by means of two bakers of eight infra-red radiators each. The environmental temperature was brought up to 115 to 120 F. At the end of ten minutes the patient was perspiring. At the end of twenty minutes he was perspiring moderately and was warm. Pruritus began to be noticeable in the perineal and inguinal regions. At the end of thirty minutes there was profuse perspiration, and urticarial wheals began to be evident all over the body. The face was flushed, grade 4, graded on the basis of 1 to 4. There was a distinct circumoral pallor. The oral temperature rose to 99.8 F. In another five minutes the urticaria was as severe as it had ever been in the patient's experience. The blood pressure remained in the region of 110 systolic and 66 diastolic but the pulse rate became elevated to 104 beats per minute. After another ten minutes the urticaria was maximal. The attack subsided in about one hour.

On April 27, 1945 our patient, together with 2 control patients, was subjected to a warm environment, the temperature starting at 70 F. and gradually increasing to 100 F. The patients were seated in a quiet room. The purpose of this experiment was to see whether our patient's sweating mechanism was functioning normally. To determine the degree and distribution of the sweat pattern the colorimetric technic of Silverman and Powell [3] was used. It was noted that all 3 patients showed normal palmar sweat responses. Within five minutes (room temperature 75 F.) dark stains, indicative of sweating, were visible over the finger tips and palms. At this time no demonstrable sweating was seen over the rest of the body. However, at the end of half an hour (room temperature 83 F.) both control patients, but not the allergic patient, were showing generalized sweating (extremities, chest, neck). The sweating of the 2 controls kept increasing as the environmental temperature was raised. In the meantime, our allergic patient was free of any evidence of sweating, except for the palms, soles and axillas and slightly on the forehead. At the end of two and three-quarter hours, when the temperature outdoors reached 98 F., our patient broke out rather suddenly in generalized body sweating. At this period the intensity and the distribution of the sweat pattern were equal in all 3 patients.

3. Silverman, J. J., and Powell, V. E.: A Simple Technic for Outlining the Sweat Pattern, War Med. **7**:178 (March) 1945.

Our patient under experimental conditions demonstrated a definitely diminished response in generalized body sweating. Under prolonged or intense stimulation, however, a normal response was obtained. Palmar sweating was perfectly normal.

(*b*) Local Heat: On April 5, 1945 the left forearm and arm were immersed in water having a temperature of 110 F. for ten minutes. There was no effect locally on the skin and none on the blood pressure or pulse rate. No urticaria was produced.
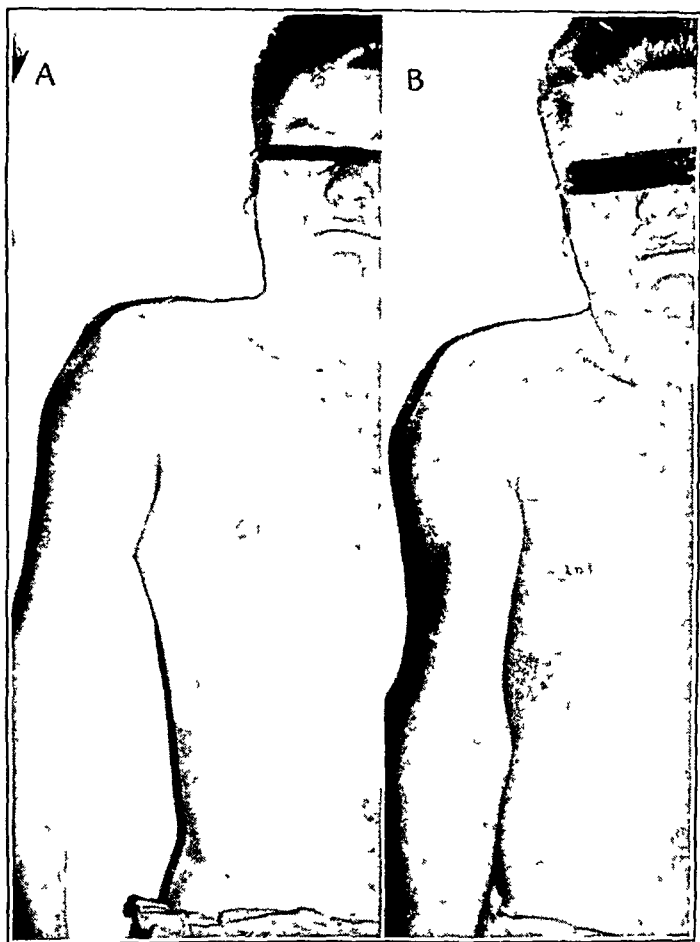
Fig. 3—*A*, patient before exercise; *B*, patient after exercise. (United States Army Signal Corps photograph.)

On April 6, 1945 a test tube of hot water was placed on the skin of the left forearm. After ten minutes there was no evidence of local urticaria, itching or general reaction.

Application of heat over a localized area was unsuccessful in producing an urticaria. It should be noted, however, that we were dealing with local stimuli of insufficient strength to affect the general body temperature.

(*c*) Exercise: On March 20, 1945 and on twelve other occasions on different days, the patient was asked to run for a period of fifteen minutes. During each exercise he covered approximately 2,500 yards (2,200 meters). At the end of that time and within the succeeding ten minutes, it was noticed that a generalized urticaria appeared, associated with considerable pruritus and wheals varying in size from that of a match head to that of a thumb nail. The face became noticeably flushed and swollen (fig. 3 *B*), and there was an intense erythema over the neck, shoulders and chest. In addition, there was a characteristic circumoral pallor. The pulse rate and blood pressure were elevated but were within normal limits. Later, after the eruption occurred, the blood pressure dropped to as low as 88 systolic and 50 diastolic. This usually occurred about fifteen to thirty minutes after the eruption became maximal. In approximately one to one and one-half hours the urticaria as well as the pruritus disappeared entirely, and the circulatory system returned to normal.

· Studies on the refractory phase. Study after one hour: On April 4, 1945 the patient was exercised for fifteen minutes, and an urticaria developed as described previously. One hour later the patient was again exercised, but no eruption occurred over the body. It appeared as though the patient was in a refractory phase.

Study after three hours: On April 10, 1945 the patient was exercised again in the usual manner, and afterward the skin broke out with typical urticaria. Three hours later he was again exercised in a similar fashion, but this time the skin did not break out in wheals. Apparently the patient was still in a refractory phase, during which it was impossible to provoke an urticarial reaction by the stimulus of exercise. A white blood cell count with a differential count was taken before and after the first exercise. The results are shown below:

	White Blood Cell Count	Differential Polymorpho-nuclears	Lymphocytes	Eosinophils
Before exercise...................	10,600	45%	50%	5%
After exercise...................	16,000	47%	47%	2%
		and 2% monocytes and 2% basophils		

Apparently the production of the urticaria is not associated with a rise in the eosinophilic cells.

At the height of the urticarial reaction following exercise, a photograph was taken, showing the type of response (fig. 4). A photograph of the skin was taken before exercise for the sake of comparison (fig. 5). Figure 3 is a composite picture showing more of the body before and after exercise performed on another occasion.

Study after five hours: On April 20, 1945 the patient was exercised again in the usual fashion, and subsequently the typical urticaria, pruritus, facial cervical and shoulder flush were observed. In addition, the scrotum and penis became swollen. Five hours later he was again exercised. He had a facial flush after this exercise but only slight pruritus and a few scattered wheals. The latter were mild but definite over the chest, abdomen and shoulders.

Apparently it is possible in five hours to reproduce the urticaria in this patient, but it is not possible to do so during the absolute refractory period of three to four hours following a typical urticarial response induced by exercise. The urticaria induced at the end of five hours was

mild, indicating that the patient may have been in a relative refractory period at the time.

(*d*) Cold: On April 3, 1945 the patient was taken inside a large refrigerator, the temperature of which was between 48 and 50 F. He was kept in there for twenty minutes. No external changes occurred, and no urticaria and no pruritus were noticed after exposure to this environment.

On April 12, 1945 ice cubes were applied to the skin of the right forearm for one minute. No unusual reaction and no wheals occurred as are found to occur in patients allergic to cold.
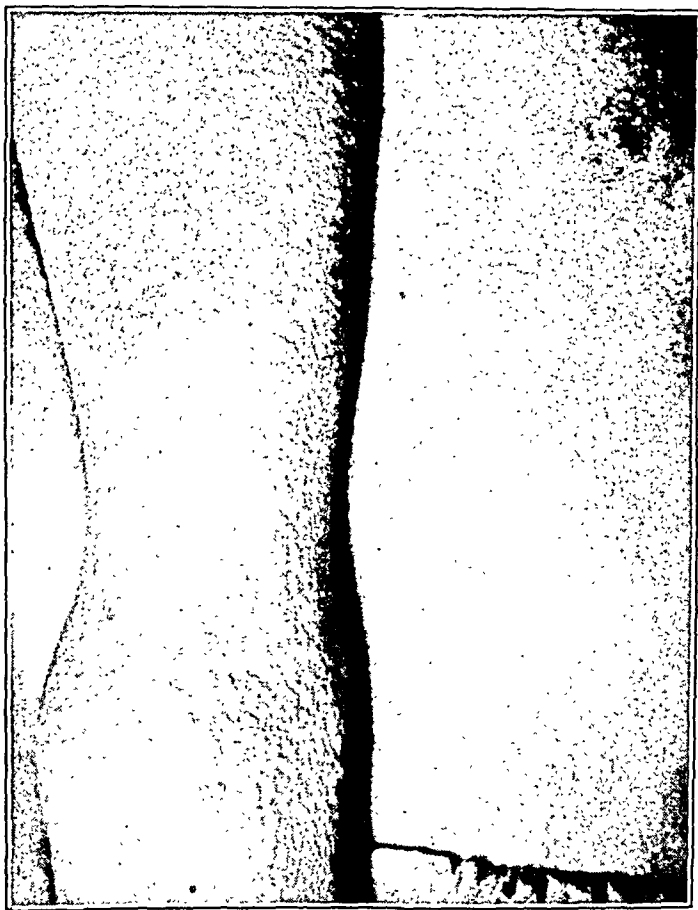
Fig. 4.—Urticaria after exercise. (United States Army Signal Corps photograph.)

This patient showed no evidence indicating allergy to cold.

(*e*) Pressure: On numerous occasions we were able to demonstrate the response of the skin to stroking with a blunt object. A typical dermatographic response became evident within three to five minutes, demonstrating the triple response of Lewis, that is, the white line, then the wheal and the flare about the zone of stimulataion.

2. *Gastric Analyses.*—On March 22, 1945, 100 cc. of 7 per cent ethyl alcohol was introduced into the patient's fasting stomach. No free hydrochloric acid was produced.

On March 27, 1945 another 100 cc. of 7 per cent ethyl alcohol was introduced into the fasting stomach, and again no free hydrochloric acid was obtained. A gastric analysis immediately after exercise failed to show any free hydrochloric acid one-half hour after the urticaria was induced.

On March 29, 1945 histamine phosphate given intravenously (1 : 250,000) and subcutaneously (1 mg. per cubic centimeter) brought forth free hydrochloric acid up to as high as 60 units and the total acids up to 65 units.

On March 30, 1945 an attack of generalized urticaria was induced by exposure of the patient to radiant heat for one-half hour as previously described. Gastric
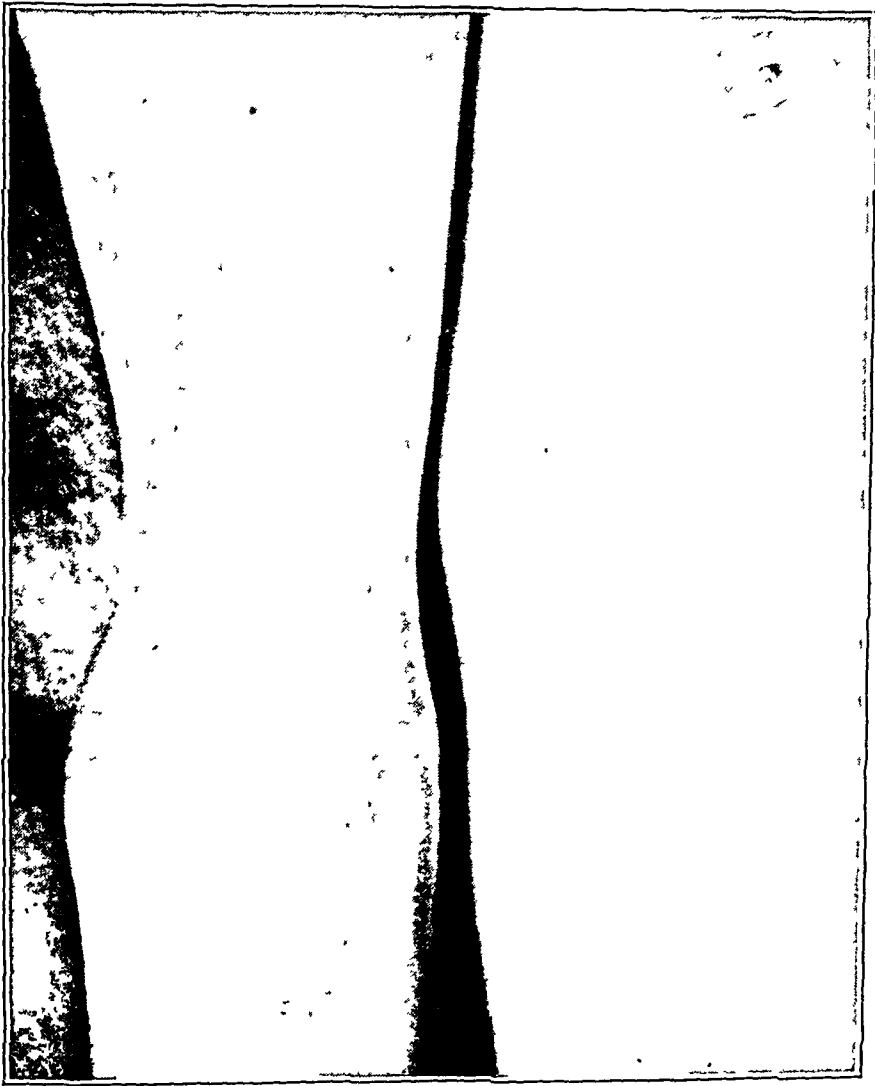
Fig. 5.—No urticaria before exercise or heat. (United States Army Signal Corps photograph.)

analyses for one hour after the eruption failed to reveal the presence of any free hydrochloric acid. Specimens were taken at fifteen minute intervals.

Alcohol, exercise and heat failed to evoke a free hydrochloric acid response. Histamine phosphate, however, gave a prompt response. This problem will be further discussed under "Histamine."

3. *Effect of Drugs.*—Intradermally: A small amount of histamine phosphate (0.10 cc. of a solution containing 1 mg. per cubic centimeter) was injected

intradermally into the skin of the forearm. Within fifteen minutes a typical wheal with pseudopod formation became evident, surrounded by a zone of erythema 2 to 3 inches (6 to 7.6 cm.) in diameter. The wheal was 1 by 1.5 cm. in diameter. The pseudopod portion was about 0.5 cm. long.

Subcutaneously: Four-tenths cubic centimeter of the same histamine phosphate solution produced little effect on the patient. It caused a slight rise in the gastric acids, bringing out free hydrochloric acid, as described under gastric analysis. A slight wheal and some erythema occurred about the site of the injection, but no systemic response was noted.

Intravenously: On March 31, 1945 an intravenous injection of histamine phosphate (1 : 250,000 solution) was given at a rate of 170 to 200 drops per minute. A total of 200 cc. of the solution (histamine phosphate in isotonic solution of sodium chloride) was given in about twenty minutes. A typical histamine flush of the face, neck, shoulder and upper part of the chest occurred. Around the mouth was a pronounced pallor. No urticaria was observed. The blood pressure did not fall appreciably, although the pulse became accelerated to approximately 100 beats per minute. At the height of the injection—i. e., at the maximal rate of flow—the patient complained of a moderate headache. Specimens of gastric juice were collected at regular intervals, and they showed increasing amounts of free and total hydrochloric acid.

Apparently the gastric mucosa was rather resistant to stimulation, ethyl alcohol having failed on two occasions to provoke free hydrochloric acid. In such circumstances a diagnosis of achlorhydria would have been made. The use of histamine subcutaneously or intravenously as a diagnostic agent is indicated before such a diagnosis is considered. The latter route is the most powerful way of stimulating the gastric mucosa.

Refractory Phase Study (Histamine): On April 18, 1945 the patient was given 250 cc. of a 1 : 250,000 solution of histamine phosphate at a rapid rate of 105 to 200 drops per minute. The systolic blood pressure did not fall more than 8 to 10. No urticaria developed, but there did appear a pronounced erythema on the face, neck, thorax, abdomen and upper extremity. This erythema showed up at first in little spots which later coalesced to form a generalized reddening of the skin. A circumoral pallor was noted. A moderate headache developed.

After the injection was completed, the patient was exercised in the usual fashion for fifteen minutes. Subsequently an urticarial response was induced, but it seemed to be not so prominent as under ordinary exercise. The eruption was about 75 per cent as prominent over the chest and abdomen as that which develops after exercise only.

The injection of histamine phosphate intravenously before exercise may have had a slight inhibitory effect on the development of subsequent urticaria.

(b) Epinephrine: On April 11, 1945 epinephrine hydrochloride, 0.4 cc. of 1 : 1,000 solution, was injected subcutaneously just before exercise was begun, and seven minutes later a similar quantity was injected midway during the exercise. At the end of the exercise period of fifteen minutes, the patient was observed for nearly an hour. No urticaria, pruritus or any kind of allergic response usually seen after exercise in this patient was observed. The blood pressure was observed to rise to 170 mm. of mercury systolic just after exercise, but this dropped in three minutes to 135 mm. of mercury. The pulse rate remained around 112 beats per minute for fifteen minutes following the exercise.

Epinephrine injected before and during exercise prevented the development of urticaria following exercise.

(*c*) Ephedrine Sulfate: On April 22, 1945 the patient was given ephedrine sulfate, 45 mg. by mouth every four hours for four doses. The patient was then exercised in the usual fashion for fifteen minutes. A typical outbreak of urticaria developed.

Ephedrine sulfate in the dose and frequency employed apparently was ineffective in preventing the urticarial outbreak.

(*d*) Atropine Sulfate: On April 7, 1945 the patient was given ⅓₅ grain (0.8 mg.) of atropine sulfate subcutaneously. He was then exercised for fifteen minutes in the usual fashion. The drug did not prevent the breaking out of the urticaria, but the rash appeared to be definitely milder. The drug did not prevent the facial flush or the circumoral pallor. Following the exercise the blood pressure was observed to fall to 90 systolic and 66 diastolic, but the pulse rate remained elevated. There was little sweating. The oral temperature became elevated to 100.4 F.

On April 9, 1945 the patient was given a stronger dose of atropine sulfate (⅓₅₀ grain [1.2 mg.]) and then exercised as before. This time the breaking out of the urticaria was delayed for half an hour, and when it did come it was minimal. No sweating was observed, but there was a facial flush and mild pruritus. The oral temperature rose to 101 F. The blood pressure rose no higher than 120 systolic and 65 diastolic, and the pulse rate rose as high as 160 immediately after exercise. The mild urticaria disappeared almost completely at the end of fifty minutes.

Atropine sulfate had a definite inhibitory effect on the production of urticaria following exercise.

(*e*) Pilocarpine: The patient was given 1/12 grain (5 mg.) of pilocarpine hydrochloride on April 12, 1945, and the effect was observed systemically. There was no effect on the blood pressure or pulse. The face became warm and flushed; salivation and perspiration were produced, but no urticaria or pruritus was noted. There was a slight fall in the oral temperature. Twenty-five minutes after the injection of the drug, when it appeared that no urticaria was going to develop, a new drug called Furmethide,[4] whose action is similar to that of acetylcholine, was given in a dose of 5 mg. subcutaneously. Seventeen minutes later a definite mild urticaria was observed, the wheals being of about pinhead size. This drug also produced some tightness in the chest, some rales, sweating, salivation, lacrimation, urination and a pronounced facial flush. The wheals started fading out in about thirty to forty minutes.

It is possible that the effect of the pilocarpine had not worn off completely and that when Furmethide was given the combined effect of the two drugs was able to provoke an urticarial response, for, as reported in subsequent paragraphs, Furmethide alone on other occasions failed to bring out any urticaria.

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4. Furmethide is chemically related to acetylcholine and is the proprietary name for furfuryl trimethyl ammonium iodide. This drug was supplied by Smith, Kline & French Laboratories, Philadelphia.

(*f*) Furmethide (furfuryl trimethyl ammonium iodide): On April 21, 1945 the patient was given 5 mg. of Furmethide alone subcutaneously, and the effect was observed. The pulse rate was increased from 68 to 100, but there was no effect on the blood pressure. Increased warmth, flushing of the face, lacrimation, pronounced sweating, urination of 400 cc. and scrotal and facial pruritus were noted. No urticaria was observed.

Furmethide alone did not produce urticaria.

(*g*) Furmethide and Histamine: On April 16, 1945 it was thought on the basis of the previous studies that the injection of both histamine and Furmethide might bring out the urticaria. Therefore, 0.4 cc. of histamine phosphate (1 mg. of histamine per cubic centimeter) was given subcutaneously along

Fig. 6.—Region of right shoulder, demonstrating urticaria produced by simultaneous injection of histamine phosphate and Furmethide.

with 2.5 mg. of Furmethide After an interval of fifteen minutes, when no urticaria was observed, another 2.5 mg. of Furmethide was given, followed by another dose of 0.4 cc. of histamine phosphate ten minutes later. Within ten minutes of the last injection an urticaria began to be evident and progressed in extent until it became similar to that produced by exercise or external heat.

On April 19, 1945 the same drugs were used as in the previous experiment, but this time 0.4 cc. of histamine phosphate and 5 mg. of Furmethide were injected simultaneously into opposite arms. There developed tightness in the chest, flushing of the face, watering of the eyes, sweating of the hands and face and a moderate headache. In about ten minutes following the injection an urticaria began to develop over the body, which increased, the wheals coalescing and becoming larger. At this period there was considerable pruritus in the

perineal, cephalic and shoulder regions. It required about half an hour for the rash to come out to its maximal extent, and when it did it compared favorably with the generalized eruption produced by exercise alone (fig 6). Unfortunately, the photograph shows the poorest result obtained.

On April 18, 1945 the same two drugs were used in a control patient (nonallergic) in exactly the same manner as described in the experiment of April 16, 1945. No effect was observed on the blood pressure; the pulse rate became somewhat elevated, and the oral temperature fell from 98.4 to 97.8 F. There were considerable sweating and flushing of the face, as well as sweating of the palms. At no time was any urticaria produced.
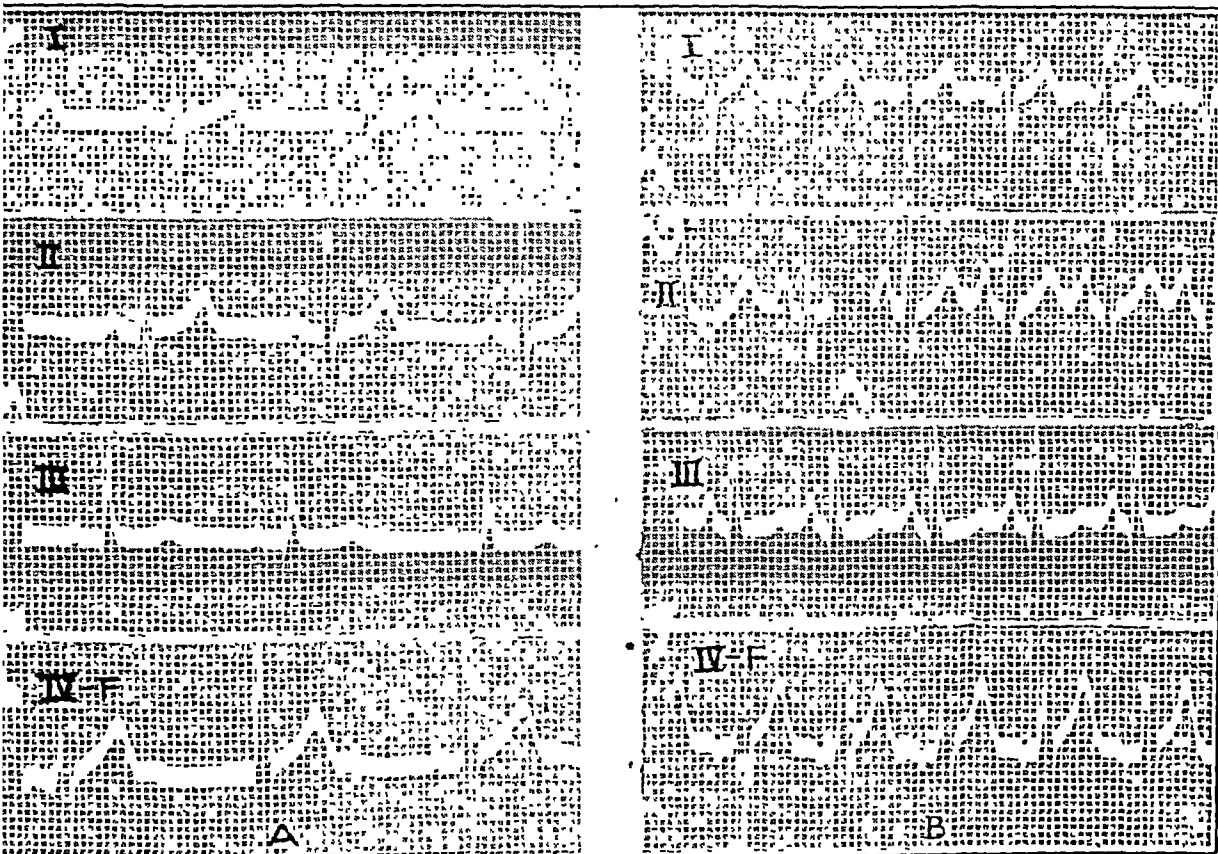
Fig. 7.—Electrocardiograms. *A*, taken at rest before test; *B*, taken at height of urticaria. Note changes in P and T waves. There is also an increase in the deviation of the electrical axis to the right.

On two occasions the use of histamine phosphate and Furmethide together produced a definite urticaria. The same drugs used in a similar manner in a control patient were ineffectual in producing an urticaria.

4. *Electrocardiographic Studies.*—Cardiac disorders, including angina pectoris, tachycardia and ventricular extrasystoles, have been attributed to heat allergy.[5]

, 5. Duke, W. W.: Relationship of Heat and Effort Sensitiveness and Cold Sensitiveness to Functional Cardiac Disorders Including Angina Pectoris, Tachycardia, and Ventricular Extrasystoles, J. Allergy 4:38, 1932.

To investigate this problem, electrocardiograms were taken on this patient a number of times and at frequent intervals before exercise, after exercise and after the urticarial eruptions. An electrocardiogram taken before and one taken at the height of the urticaria are shown (fig. 7). A right axis deviation was noted, which seemed to be more pronounced during the urticaria. In addition, there was a sinus tachycardia and the P and T waves seemed to be more pronounced.

In general, one might say that no real significant changes were noted. No arrhythmias or signs of coronary insufficiency were found.

5. *Neuropsychiatric Studies.*—Since there is often a psychogenic element in cases of urticaria, this patient was referred to the psychiatric department of the hospital for a detailed study.[6] An attempt was made to induce urticaria by hypnosis. Narcosynthesis with sodium amytal was also tried. Attempts to reproduce the urticaria by these psychiatric technics were totally unsuccessful. Furthermore, the neuropsychiatric survey failed to reveal any history of neuropathic stigmas, neurotic traits or other emotional or psychologic abnormalities. In fact, the patient was found to have a stolid and placid attitude toward his illness. To quote the psychiatrist, "It is believed that this illness is purely organically conditioned. It is felt that this is one type of somatic illness not amenable to psychotherapy." Finally, a Minnesota psychometric test was performed. The results were entirely within normal limits.

COMMENT

This case presented several interesting phenomena, in addition to being a clinical instance of physical allergy, or more specifically, heat allergy. An attack of urticaria was easily produced experimentally by a fixed form of exercise. Following the urticaria produced by the exercise, a refractory period was found. This refractory period lasted for approximately five hours. Thus, if the patient exercised again an hour or two after the subsidence of the rash a normal response was obtained, that is, no urticaria occurred; and if he exercised again at the end of five hours only a slight urticarial reaction occurred. This refractoriness, or unresponsiveness, as Grant, Pearson and Comeau [2] have preferred to call it, has been observed by others.[7] The mechanism operating in this state of immunity is not clear. Results of our studies with epinephrine and atropine suggest that during the refractory period certain related chemical substances or enzymes are released which bring about a temporary state of refractoriness or unresponsiveness.

This study further demonstrated that exercise was not essential in the production of the urticarial response. Application of external heat

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6. Capt. Luis Perelman, Medical Corps, Army of the United States, performed the psychiatric studies.

7. Marchionini, A., and Ottenstein, B.: Schwitzurticaria: Physikalisch-Chemische Untersuchungen zur Pathogenese urticarieller Erkrankungen, Arch. f. Dermat. u. Syph. **163**:61, 1931; cited by Grant, Pearson and Comeau.[2]

brought forth an urticaria in no way different from that produced by exercise. It has been observed by others [8] that the reaction of sensitivity to heat may vary in the type of response and intensity. In some patients the reaction may be chiefly constitutional, and Duke [8a, b] expressed the opinion that in many cases heat prostration and neurocirculatory asthenia are basically problems of sensitivity to heat. Wolkin and his associates [9] have recently studied a group of soldiers training in the desert who were found to be intolerant to excessive heat. In these soldiers there was a failure of the sweating mechanism. These investigators pointed out that this group should be differentiated from those suffering with heat stroke, heat exhaustion and heat cramps. In many patients on exposure to heat less pronounced reactions, such as a thermic headache, erythema or a few hives, are commoner. It is surprising in how many people these milder reactions develop.[8c]

The sensitive response of the gastric mucosa to histamine is a well known fact. The mechanism in cold allergy has been shown [10] to be essentially a release of histamine and has been effectively treated from this standpoint. In cold allergy, the mechanism of which seems in many ways allied to that of heat allergy, Horton, Brown and Roth [10] demonstrated a distinct rise in gastric acidity. In our patient the failure to show any free hydrochloric acid after exercise or after the application of heat would seem to negate the concept that histamine is released in heat allergy. It should be realized, however, that we were dealing with a gastric mucosa rather resistant to stimuli. Ethyl alcohol, a known gastric stimulant, was also unsuccessful. No definite conclusion, therefore, can be drawn from our study on gastric acidity.

During an attack of urticaria there are definite changes in the dynamics of the circulation. Duke [5] observed angina pectoris, tachycardia and cardiac arrhythmias following heat allergy. Depending on the rapidity and degree of exudation of serum into the skin, changes in the volume of blood are to be expected. In addition, there is also evidence of peripheral vasodilatation. The pronounced flushing of our patient was a feature constantly observed. Peripheral vasodilatation is

8. Duke, W. W.: (a) Heat and Effort Sensitiveness: Cold Sensitiveness, Arch. Int. Med. **45**:206 (Feb.) 1930; (b) Clinical Manifestations of Heat and Effort Sensitiveness and Cold Sensitiveness, J. Allergy **3**:257, 1932. (c) Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679 (Nov.) 1938.

9. Wolkin, J.; Goodman, J. I., and Kelley, W. E.: Failure of the Sweat Mechanism in the Desert: Thermogenic Anhidrosis, J. A. M. A. **124**:478 (Feb. 19) 1944.

10. Horton, B. T.; Brown, G. E., and Roth, G. M.: Hypersensitiveness to Cold, J. A. M. A. **107**:1263 (Oct. 17) 1936.

seen with both histamine and acetylcholine. The increase in pulse rate, the drop in blood pressure and the shocklike picture seen at the height of the urticaria in our patient simulated closely the condition observed by Weiss, Robb and Ellis [11] following injections of histamine into human beings. These investigators found that intravenous injections of large doses of histamine phosphate increased the cardiac output, decreased the volume of blood and increased the mean velocity of the flow of blood. These changes were interpreted as being not the result of direct cardiac stimulation but rather a compensatory mechanism to the vaso-dilatation. That no significant changes were observed electrocardiographically in our patient is understandable when one considers that we were dealing with a young patient with good cardiac reserve. The increase in voltage of the T wave observed at the height of the urticaria may represent the normal condition after exercise.[12] Weiss and his associates [11] commented on the close simulation that exists between the circulatory responses that follow exercise and those that follow injections of histamine.

Studies dealing with urticaria are often complicated by psychogenic factors. The importance of psychic stimuli in producing urticaria has been well established.[13] Gellhorn [14] has recently shown that emotional excitement evokes both adrenergic and cholinergic responses. Partly as a result of Cannon's work [15] most of the attention has been centered on the adrenergic responses. However, during emotional excitement the cholinergic system is also active. Excessive palmar sweating is a striking example of a cholinergic response seen in anxiety states.[16] However, we believe that we have satisfactorily eliminated any criticism that psychogenic factors were important in the genesis of the urticaria seen in our patient.

11. Weiss, S.; Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, with Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (March) 1932.

12. Hartwell, A. S.; Burrett, J. B.; Graybiel, A., and White, P. D.: The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram, with Particular Reference to T Wave Changes, J. Clin. Investigation **21**:409, 1942.

13. Stokes, J. H.; Kulchar, G. V., and Pillsbury, D. M.: Effect on the Skin of Emotional and Nervous States, Arch. Dermat. & Syph. **31**:470 (April) 1935.

14. Gellhorn, E.: Autonomic Regulations, New York, Interscience Publishers, Inc., 1943.

15. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 2, New York, D. Appleton and Company, 1929.

16. Silverman, J. J., and Powell, V. E.: Studies on Palmar Sweating: II. The Significance of Palmar Sweating, Am. J. M. Sc. **208**:297, 1944.

Studies on the patient's sweat mechanism were revealing. Although the patient stated that he thought that he perspired somewhat less than others, at first he appeared to sweat normally while under the heat radiators. However, when he was tested under more controlled experimental conditions, he showed a definitely delayed sweating response over his general body surface. Palmar sweating at all times was found to be perfectly normal. Generalized body sweating differs from palmar sweating on anatomic and physiologic grounds.[16] Generalized body sweating, and not palmar sweating, is concerned with the thermoregulatory mechanism, and it is this type of sweating that was found at fault. Although detailed studies on temperature were not made, the evidence suggests that there was some inherent defect in this patient's thermoregulatory system. Duke [8a, h] attacked the problem from this standpoint and was able to effect cures by improving the thermoregulatory mechanism. Horton [17] also has observed changes in the sweat mechanism of patients with heat allergy and in these patients a diminished sweating response was observed on exposure to heat.

It would seem that in certain patients with a disturbed thermoregulatory mechanism on exposure to heat or following exercise certain chemical substances related to histamine and acetylcholine are released, which set off an urticarial reaction. Evidence for this is shown in the experimental data. Atropine sulfate, a powerful anticholinergic drug, is found to have a definite inhibitory effect on the development of the urticaria. The greater the dose of the drug the less was the urticarial response, and the more delayed was it in developing. Epinephrine, the antagonist of histamine, injected before and during exercise prevented the urticaria and pruritus from developing. Although pilocarpine and choline derivatives have been successfully employed in producing an urticaria,[18] neither Furmethide nor pilocarpine hydrochloride in the doses given was successful in producing an urticaria in our patient when given alone. Similarly, histamine phosphate, whether injected intravenously or subcutaneously, by itself produced no urticaria. However, it is only fair to mention that the drug given intravenously prior to exercise appeared to have a slight inhibitory effect on the production of the urticaria. But when histamine phosphate and Furmethide, a choline derivative, were injected together, a definite urticaria was obtained each time this combination was used. In a normal control these two drugs combined produced no urticaria.

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17. Horton, B. T.: *Personal communication to the authors.*

18. Grant, Pearson and Comeau.[2]   Hopkins, Kesten and Hazel.[8c] Marchionini and Ottenstein.[7]

It, therefore, seems likely to us that both histamine and acetylcholine-like substances play a role in the physiochemical background underlying the type of heat allergy seen in this patient. This hypothesis, first proposed by Grant and his co-workers,[2] does not seem unreasonable when one considers that histamine is a normal constituent of the cells of the body and acetylcholine is always released during stimulation of an efferent nerve. Dale, Feldberg and Vogt [19] in 1936 showed that acetylcholine was released at the motor nerve end plates associated with voluntary striated muscle. The release of both histamine and acetylcholine in the body is probably going on all the time but is kept under control by neutralizing enzymes. It is conceivable that in our patient these enzymes, histaminase and cholinesterase, were present in insufficient amounts. In a patient with an inherent defect of the thermoregulatory system, it is possible that on exposure to sufficient heat or exercise more than the usual amount of acetylcholine is released to bring about sufficient sweating. Sweating is the main mechanism by which the body is cooled. The body may overcompensate, so to speak, as it so often does, to attempt to correct a defect. At the same time histamine is also released, and the two substances together bring about an urticarial response in a fashion similar to that produced experimentally. Figure 1 shows graphically the concept of the probable relationship of the various factors operating in the urticarial response in our patient.

It was not possible to carry out a satisfactory therapeutic program, as our patient was discharged from the army. On the basis of our studies, however, possibilities in the way of therapy should be considered. While desensitization with histamine or with acetylcholine is the logical form of treatment, it appears to us that the combined use of the two drugs would provide a still better method of treatment. Other avenues of approach, dealing particularly with the heat-regulatory mechanism, should be mentioned. Thyroid extract elevates the basal metabolic rate and has been used successfully in this condition.[8a] Also injections of foreign proteins, such as typhoid-paratyphoid combined vaccine, characteristically affect the thermoregulatory mechanism and might be tried. That a state of unresponsiveness can be induced is indicated by our studies dealing with the refractory period found after repeated exercise. Desensitization, therefore, should be considered in the form of a program of graduated exercise or of increased exposure to moist or dry heat in a manner similar to the desensitization for cold allergy.

19. Dale, H. H.; Feldberg, W., and Vogt, M.: Release of Acetylcholine at Voluntary Motor Nerve Endings, J. Physiol. **86**:353, 1936.

SUMMARY AND CONCLUSIONS

The case of a patient with a physical allergy (heat and exercise) is presented.

The mechanism in this type of allergy can be demonstrated better on the basis of both histamine and acetylcholine than on the basis of one chemical substance alone.

Desensitization with both histamine and acetylcholine is proposed as a method of treatment.

CHRONIC HEMOLYTIC ANEMIA

Observations on the Effect of Fat Content of the Diet and Multiple Red Cell Transfusions

ROBERT S. EVANS, M.D.

SAN FRANCISCO

A COMPREHENSIVE review of the present knowledge concerning the hemolytic disorders has recently been presented by Davis.[1] While many acute and chronic forms of hemolytic anemia can now be recognized as disease entities, in a large proportion of the cases observed here in recent years no familial factor, etiologic agent or hemolytic system could be demonstrated. This group of cases has usually been described under the heading of acquired hemolytic anemia. Dameshek and Schwartz [2] have emphasized the acute and subacute course of the disease but have recognized more chronic forms. These authors were able to demonstrate isohemolysins in the blood of 3 patients,[3] but the presence of such substances in the circulation, as determined by tests in vitro, must be a rare occurrence.[4] Autohemolysins have not been demonstrated, though autoagglutinins active at body temperature have been reported.[5]

Further study of patients with acquired hemolytic anemia is particularly important because of the unpredictable response to splenectomy that has been observed in this group. While some observers have reported a high percentage of good results, others have had less success. At the present time there are no criteria for predicting whether this major operation will be successful or futile in the individual case.

1. Davis, L. J.: Haemolytic Anaemias, Edinburgh M. J. **50**:589 (Oct.) 1943.

2. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia, Medicine **19**:231 (May) 1940.

3. Dameshek, W., and Schwartz, S. O.: The Presence of Hemolysins in Acute Hemolytic Anemia, New England J. Med. **218**:75 (Jan. 13) 1938.

4. Mason, V. R.: Acquired Hemolytic Anemia, Arch. Int. Med. **72**:471 (Oct.) 1943.

5. Reisner, E. H., Jr., and Kalkstein, M.: Auto-Hemolysinic Anemia with Auto-Agglutination: Improvement After Splenectomy, Am. J. M. Sc. **203**:313 (March) 1942. Evans, R. S.: Acute Hemolytic Anemia with Auto-Agglutination: A Case Report, Stanford M. Bull. **1**:178 (Aug.) 1943.

During the past several years my colleagues and I have had the opportunity to follow the course of 2 patients whose hemolytic anemia has been chronic and fairly severe. Both patients have undergone splenectomy with some evidence of benefit, but the anemia, along with signs of increased destruction and formation of blood, has persisted. In spite of similarities in the course of the disease one difference which seems of fundamental importance has always been present. The erythrocytes of one patient have always shown spherocytosis and increased fragility in hypotonic saline solution, while the erythrocytes of the other have persistently exhibited a normal resistance to hemolysis in hypotonic saline solution and an absence of spherocytosis. Studies of the rate of destruction and formation of erythrocytes were undertaken in the hope of demonstrating further fundamental differences between these patients.

Johnson and his colleagues [6] have recently called attention to the importance of lipemia in destruction of erythrocytes, and previous measurements [7] have shown that the output of urobilinogen of human infants is increased with a diet high in fat content. It seemed possible that in the presence of accelerated destruction of red cells the fat content of the diet played an important role in the rate of hemolysis in 1 or both patients. We have attempted, therefore, to determine what effect, if any, diets of high and low fat content would have on the rate of destruction of red cells.

The introduction of normal erythrocytes into the circulation of persons with hemolytic anemia by transfusion also has aspects of theoretic and practical interest. If the survival time of transfused erythrocytes is shown to be normal, it would imply that the increased destruction of the native erythrocytes was produced by selective auto-hemolytic substance, which seems unlikely, or that a defect in cell structure exists which predisposes to a shorter life span. Interesting observations of this nature have been made by Dacie and Mollison,[8] which indicate that transfused cells have a normal longevity in familial hemolytic jaundice and a reduced survival time in acquired hemolytic anemia.

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6. Johnson, V.; Freeman, L. W., and Longini, J.: Erythrocyte Damage by Lipemic Serum in Normal Man and in Pernicious Anemia, J. A. M. A. **124**: 1250 (April 29) 1944.

7. Josephs, H. W.; Holt, L. E.; Tidwell, H. C., and Kajdi, C.: The Influence of Dietary Fat upon the Excretion of Urobilin, Bull. Johns Hopkins Hosp. **71**:84 (Aug.) 1942.

8. Dacie, J. V., and Mollison, P. L.: Survival of Normal Erythrocytes After Transfusion to Patients with Familial Haemolytic Anemia, Lancet **1**:550 (May 1) 1943.

The recent use of multiple transfusions of concentrated red cells. has permitted the restoration of the circulating hemoglobin to normal levels in a short space of time. The elimination of the anemic state in a patient with hemolytic anemia should have a profound effect by diminishing the rapid formation of blood to a normal range and consequently by *modifying one of the constant features of the disease.* In our patients, therefore, we have tried to gain indirect evidence as to the fate of transfused normal cells and to measure the rate of destruction and formation of blood following the restoration of the circulating hemoglobin to normal by transfusions of red cells.

METHODS

All hematologic determinations were done with venous blood. The mixture of ammonium oxalate and potassium oxalate described by Heller and Paul [9] was used as the anticoagulant. Determinations of hematocrit values were done by the Wintrobe [10] method. Preparations for counting reticulocytes were made with the coverslip technic, using a thin dry film of cresyl blue as the vital stain. The quantitative studies of fragility of erythrocytes in hypotonic saline solutions were done by the method of Waugh and Asherman. [11] Determinations of bilirubin in the blood were made by the method of Malloy and Evelyn. [12] The method described by Watson [13] was used in following the output of fecal urobilinogen in one patient. The other patient had an ileostomy opening, so that some trial and error were necessary before a satisfactory method of quantitating the excretion of pyrrole pigment was found. The Watson method of extraction showed that output of urobilinogen was only 10 to 15 mg. per day. Aqueous and alcoholic extracts of the excreta through the iliostomy opening gave strong color reactions with the diazo reagent, but the results were variable. However, the method of Malloy and Evelyn, [14] in which the bilirubin in a dilute sample is oxidized to biliverdin with a hydrogen peroxide reagent and the amount determined colorimetrically, yielded reproducible results and was used as follows: A two or three day collection of excreta from the artificial anus was diluted to 4,000 cc. with water and stirred with an electrically driven propeller to insure thorough mixing. A 200 cc. sample was diluted to 4,000 cc. and stirred thoroughly with the same apparatus. To

9. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anti-Coagulants, J. Lab. & Clin. Med. **19**:777 (April) 1934.

10. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte: Methods of Determination and Clinical Application, J. Lab. & Clin. Med. **17**:899 (June) 1932.

11. Waugh, T. R., and Asherman, E. G.: Use of Index of Hemolysis in Expressing Fragility of Erythrocytes, J. Lab. & Clin. Med. **23**:746 (April) 1938.

12. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481 (July) 1937.

13. Watson, C. J.: Studies of Urobilinogen: Improved Method for Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458 (Sept.) 1936.

14. Malloy, H. T., and Evelyn, K. A.: Oxidation Method for Bilirubin Determinations in Bile and Meconium with Photoelectric Colorimeter, J. Biol. Chem. **122**:597 (Feb.) 1938.

10 cc. of the dilute material 25 cc. of the hydrogen peroxide reagent and 15 cc. of 95 per cent alcohol were added. The yellow color of the solution turned to a bright greenish blue and was maximum at one hour. A sample was centrifuged, and the amount of biliverdin in the supernatant fluid was read directly in the colorimeter. The amount of pigment remaining in the small amount of sediment was found to be negligible.

REPORT OF CASES

CASE 1.—H. S. a 38 year old woman of Greek birth had undergone a colectomy for ulcerative colitis and a splenectomy for hemolytic anemia, which had continued as a chronic process. She entered the United States in 1932 and had lived in San Francisco since. Pregnancies in 1933 and 1935 were uneventful, and both children are living and well.

There is no history of illness until March 1937, when cramping abdominal pains, accompanied with diarrhea with pus and blood in the stools, began. After several months without improvement an ileostomy was done, but she continued to have an active rectal discharge. In July 1939 she was admitted to the San Francisco Hospital because of pain, swelling and tenderness in several joints. Observations relative to the joints were consistent with rheumatoid arthritis. There was an abscess about the artificial anus, and roentgenograms of the colon showed a tubular appearance with loss of haustrations. During the ensuing year a three stage colectomy was done. Pathologic examination of the specimens confirmed the diagnosis of idiopathic chronic ulcerative colitis with polypoid degeneration. No disease was demonstrated in the ileum. Her postoperative periods were complicated by parotitis and cystitis, but she gained weight and strength, and her symptoms referable to the joints subsided. She was discharged in July 1940.

An anemia which she exhibited on entry responded to iron therapy and the removal of her infected colon. There were no signs of increased hemolysis throughout her prolonged stay at the hospital.

She was next seen in the outpatient clinic of Stanford-Lane Hospital, in October 1940, because of a recurrence of her arthritis. A course of gold therapy was instituted, and injections of a 0.01 per cent solution of colloidal gold were given as illustrated in chart 1. There were no immediate reactions to the injections, but during the latter half of the course of therapy she complained of having mild abdominal pain and discomfort at intervals between injections. The leukocyte counts during the course of gold therapy showed no significant change, but the steady fall in hemoglobin is evident. As the anemia developed polychromatophilic staining of a large percentage of erythrocytes was noted in the blood smears.

Six months after cessation of gold therapy her anemia failed to improve, and she was admitted to the San Francisco Hospital, where icterus, anemia and splenomegaly were noted on admission. Reticulocytes were found to be 16 per cent of all red blood cells, and the icterus index was 20. Sternal biopsy showed normoblastic hyperplasia. During the next three months her hemoglobin continued to fall, and there was no sustained response to transfusions. Her erythrocytes showed some increased susceptibility to hemolysis in hypotonic saline solution.

Splenectomy was performed Feb. 5, 1942. The spleen weighed 450 Gm. and exhibited a thickened capsule and a soft engorged parenchyma. The spleen pulp was engorged with erythrocytes, and phagocytic endothelial cells were full of brown pigment granules. The malpighian bodies were small, and subcapsular hemorrhages were noted. The postoperative course was uneventful; her hemoglobin rose spontaneously from 38 per cent to 69 per cent of normal during the first few weeks after splenectomy, and she was discharged as improved. This period of partial remission was followed by a drop in hemoglobin to a level of 40 per cent to 50

per cent of normal, where it remained on all observations for a period of two years, except for a brief rise following transfusions. Signs of increased destruction and formation of blood have been present constantly. Reticulocyte counts have varied from 20 to 32 per cent, and nucleated, red blood cells have been noted in all blood smears. She has exhibited a constant mild icterus, and the icterus index has varied from 20 to 40. She has had mild exacerbation of symptoms referable to the joints from time to time since splenectomy, but during the last nine months her arthritis has been quiescent. She has remained ambulatory since splenectomy and able to do light housework. Her complaints of easy fatigue, weakness and dizzy sensations have been present most of the time.

Physical Examination.—At the beginning of the experimental period, on Aug. 25, 1944, some thirty months after splenectomy, her weight was 44.8 Kg. She
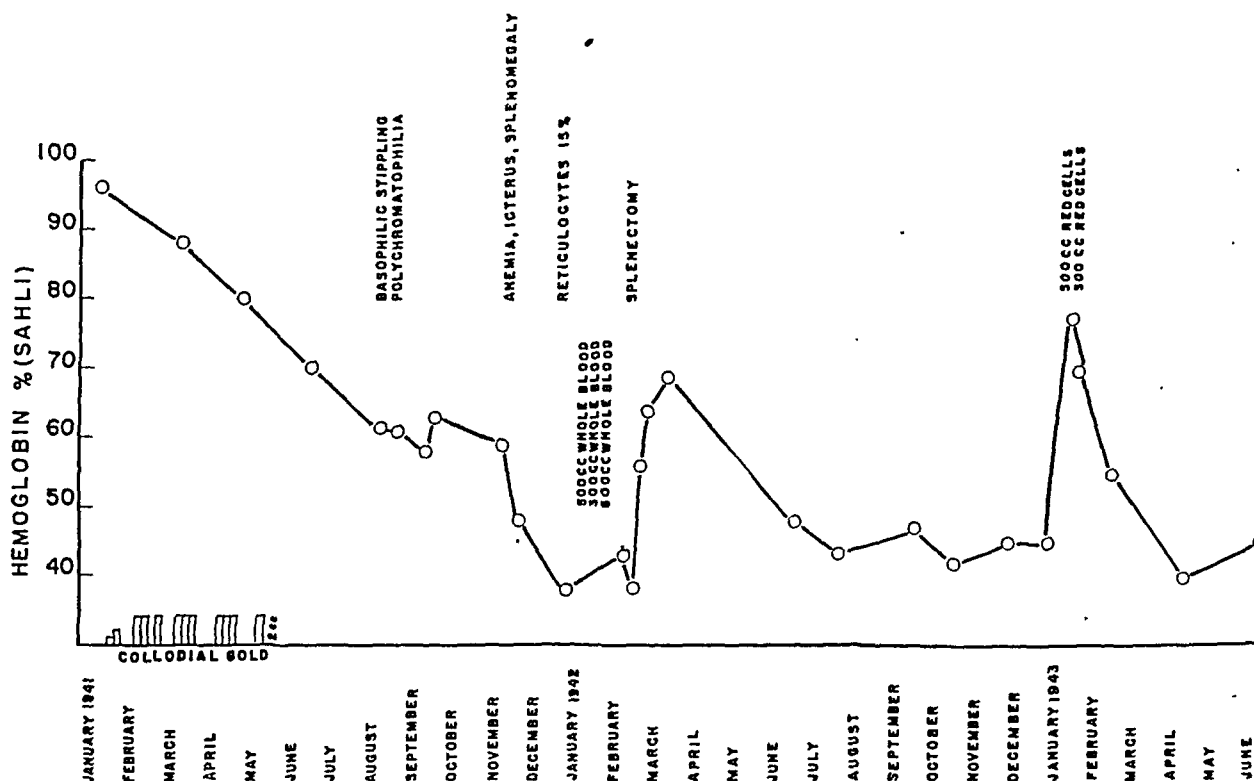
Chart 1 (case 1).—There is a steady drop in hemoglobin during and following injections of a 0.01 per cent solution of colloidal gold. Note the temporary spontaneous rise following splenectomy and the temporary rise following transfusions (two transfusions of 500 cc. of whole blood and one of 300 cc. on one occasion, and two transfusions of 500 cc. of red blood cells on another).

appeared to be about her stated age. The skin had a yellow tint, and the mucous membranes and palms were pale. There were no deformities of skull or spine. The scleras were icteric, and pupillary reactions to light and accommodation were normal. The tongue was normal. The teeth were in good repair with amalgam fillings. Tonsils were present but not remarkable. There was no general adenopathy. The thyroid isthmus was palpable but not enlarged, and the breasts were normal. The chest was clear to percussion and auscultation. The heart was not enlarged to percussion, and the rhythm was regular. There was a blowing systolic murmur along the left sternal border. The blood pressure was 85 mm. of mercury

systolic and 50 diastolic. Abdominal examination showed an ileostomy opening on the right and the colectomy and splenectomy scars. The edge of the liver could be felt at the costal margin. Previous pelvic examinations had revealed nothing abnormal. The extremities and joints were normal except for slight swelling and tenderness of the right knee joint.

Laboratory Data.—Examination of the blood at the beginning of the experimental period showed the following values: hematocrit value, 27; hemoglobin, 57 per cent Sahli (9.8 Gm. per hundred cubic centimeters of blood); erythrocytes, 2,750,000 per cubic millimeter; mean cell volume, 99 microns; mean cell hemoglobin, 35 micromicrograms; mean cell hemoglobin concentration, 36 per cent; reticulocytes, 14.5 per cent of all red blood cells, and leukocytes, 14,200 per cubic millimeter. The differential count of the leukocytes was not remarkable—57 per cent neutrophils, with 5 per cent banded forms; eosinophils, 3 per cent; monocytes, 4 per cent, and lymphocytes, 36 per cent. One per cent of nucleated cells were normoblasts. In the blood smear the erythrocytes varied greatly in size, and the most predominant cell was of smaller diameter than normal and densely stained. The other prominent cell type was of much greater diameter and usually showed polychromatophilic staining. A Price-Jones curve illustrated this great variation in cell diameter. The average cell diameter was 6.66 microns, and the average cell thickness was 3.9 microns. Susceptibility to hemolysis in hypotonic saline solution was greatly increased, as shown in chart 3. Hemolysis of the patient's cells was complete before hemolysis of normal cells began.

Her blood was of group O and was Rh positive.

The specific gravity of specimens of urine varied between 1.006 and 1.025. All specimens have shown negative reactions to tests for sugar, protein and bile. No abnormalities have appeared in the sediment. A twenty-four hour collection of urine extracted by the Watson method showed an absence of urobilinogen from the urine, a finding consistent with the small amount of urobilinogen present in the material collected from the artificial anus.

The material from the artificial anus was semisolid and weighed about 600 Gm. daily. The color varied from green to brown. No gross change in character or amount of material from the artificial anus occurred when the fat content of the diet was changed.

Experimental Data.—*Effect of Diets Low and High in Fat:* The diet history showed that she had been taking a diet relatively low in fat; hence observations were begun after a period in which the fat content and caloric intake were regulated. The data accumulated during the periods of low and of high intake of fat are presented in chart 2. As can be seen, no significant variation in hematocrit level or percentage of reticulocytes occurred. There is, however, suggestive evidence of increase in pyrrole pigment metabolism during the period of high intake of fat. The excretion of bilirubin, which averaged 680 mg. per day during the period of low intake of fat, was 780 mg. per day during the period when a diet high in fat was given. The level of bilirubin in the blood was also somewhat higher during the period in which the intake of fat was high. These differences are not significant, however, in view of the increased output of pigment demonstrated in a later control period when she was taking a diet low in fat content. At the termination of these observations a transfusion of 250 cc. of red cells was given to determine whether an increase in output of bilirubin would occur which could be measured by the method used. The excretion of 1,200 mg. per day following this transfusion is probably significant, since it is over 200 mg. higher than any previous determination.

Effect of Transfusions of Red Cells: Following an interval of fifty-two days, during which time she returned to a diet low in fat, observations as to the effect of transfusion of large amounts of red cells were begun. The data as to hematocrit level, percentage of reticulocytes and output of bilirubin in the excreta from the artificial anus are presented in chart 2.

The control period indicates that the hemolytic process was going on at a higher rate than previously. The hematocrit was at a lower level, the percentage of reticulocytes was almost twice the previous level, and the output of pigment increased to 1,000 mg. daily or more. The level of bilirubin in the blood was
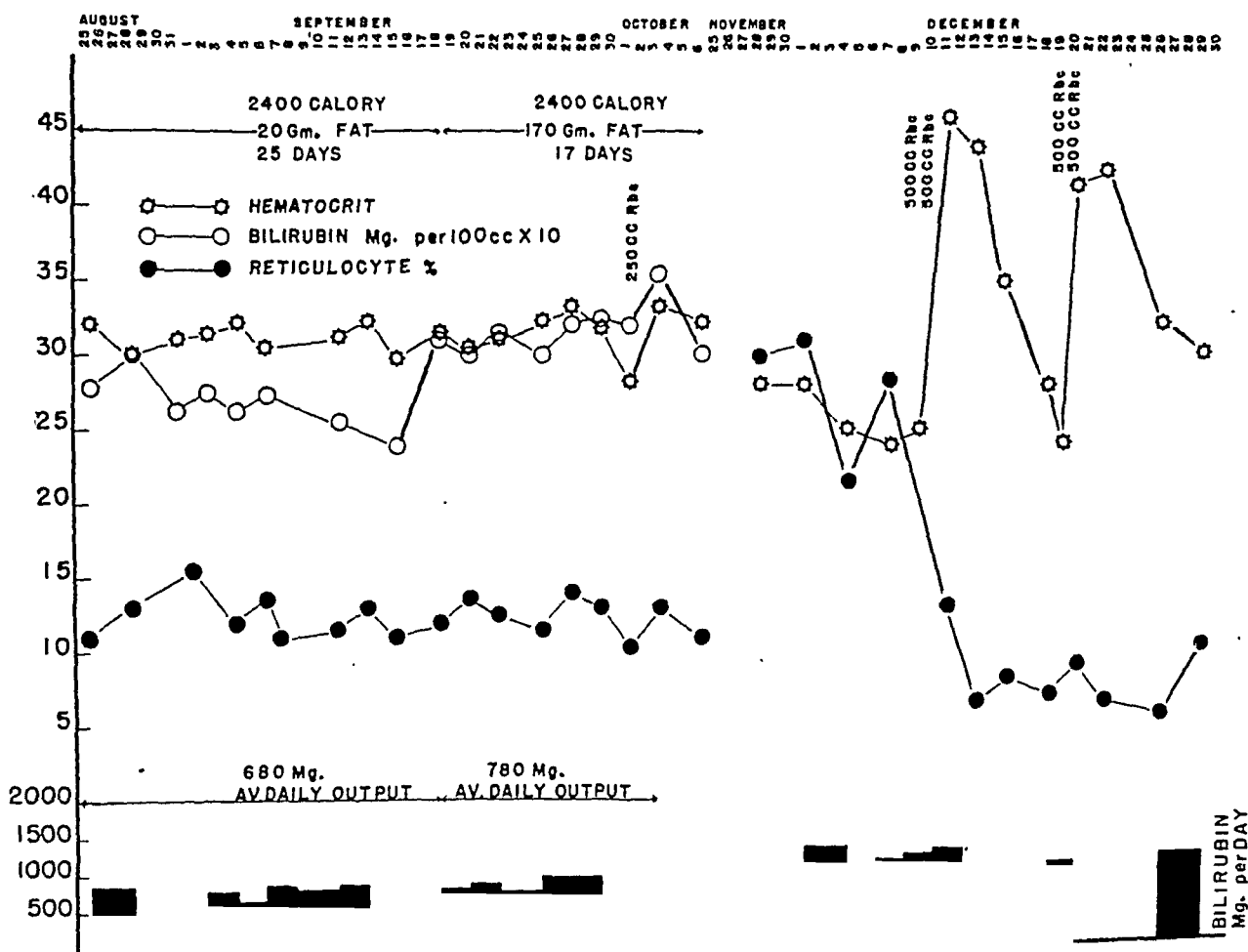
Chart 2.—Output of bilirubin in the excreta through the artificial anus from the patient with spherocytosis during periods of low and high intake of fat and following multiple transfusions of red blood cells.

also higher during this period, with levels of 5.5 mg. per hundred cubic centimeters on December 7 and 9. However, she exhibited no particular increase in symptoms as a result of the increased destruction of blood.

She was given transfusions of 500 cc. of concentrated red blood cells on two successive days without reaction. The hematocrit level was 45 the day following the second procedure. Two days after the second transfusion the curve of fragility in hypotonic saline solution was again determined and found to be nearly identical

with the curve before transfusion, even though the hematocrit level remained at 45, indicating that nearly one half the erythrocytes present were the transfused cells. There was a rapid fall in the hematocrit level following this observation, and at the end of seven days it had returned to 25, the level before transfusion. She was again given the same amount of blood in two successive procedures, and a sample of blood was taken immediately after completion of the second transfusion. Fragility curves as illustrated in chart 3 indicate a distinct shift toward normal, with 25 per cent of the hemoglobin liberated within the same range of hypotonicity in which normal cells are hemolyzed. Two days later there was a shift of the curve back to the type before transfusion, without a fall in the hematocrit value.

These observations were repeated again at a later date not shown on the chart, when a single transfusion of 600 cc. of red cells was given. There was the same shift toward normal immediately following transfusion, but observations at the end of twenty-four hours showed that the increase in fragility of the transfused
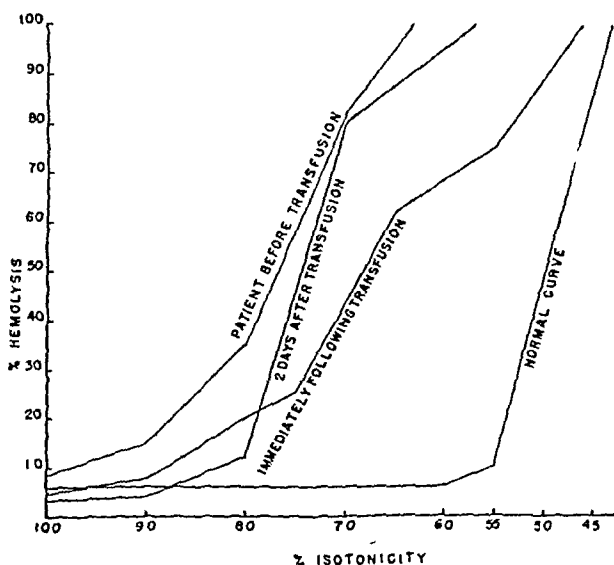
Chart 3.—Quantitative fragility curves made before, immediately after and two days following multiple transfusions of red blood cells given to the patient with spherocytosis. Immediately after transfusion 25 per cent of the red blood cells are hemolyzed within the range of hypotonicity within which normal cells are hemolyzed. A distinct shift toward the curve before transfusion occurs thereafter.

cells was largely complete in this time. Blood smears made immediately following transfusions showed a large percentage of cells with normal diameter and pale centers, while those made twenty-four and forty-eight hours later showed few if any normal-appearing mature erythrocytes in that all were lacking the pale central area. The average diameter of the nonreticulated cells was 7.7 microns following transfusion, while twenty-four hours later it was found to be 6.6 microns. The hematocrit value immediately after the transfusion was 40, and the erythrocyte counts averaged 4,460,000 per cubic millimeter. The mean corpuscular volume was therefore 90 cubic microns. In twenty-four hours the erythrocyte counts had dropped to 3,600,000 per cubic millimeter, while the hematocrit value was 38.5. According to these determinations the mean corpuscular volume had increased to 107 cubic microns. During the same twenty-four hour period the hemoglobin dropped from 13.25 to 11.9 Gm. per hundred cubic centimeters of blood.

The increase in mean cell volume accompanied by a diminished cell diameter indicates an increase in mean cell thickness or tendency toward spherocytosis. This change in cell structure was reflected in the curves of fragility in hypotonic saline solution, which are almost identical with those presented in chart 3. The close relationship between increased susceptibility to hemolysis in hypotonic saline solutions and increased cell thickness has been amply demonstrated.[15]

Attempts made to duplicate this phenomenon in vitro were not successful. Washed cells of type O from a normal person were mixed with normal serum of type O and serum from the patient in 20 per cent suspensions. Samples of these suspensions were allowed to stand at 37 C., at room temperature and at refrigerator temperature. A fourth pair was kept in constant agitation at room temperature. Fragility studies done at two day intervals showed a parallel development of increased fragility in hypotonic saline solution of the cells suspended in the patient's serum and in the control serum in all 4 instances.

These studies were repeated three times at various intervals up to thirty days following transfusion, but continued to give negative results. The addition of 0.5 cc. of guinea pig serum to each 2 cc. of cell suspension had no measurable effect.

The rapid drop in hematocrit value following the transfusions shown in chart 2 was not accompanied with clinical symptoms. Hemoglobinemia and hemoglobinuria did not appear, and there was little if any elevation of the icterus index, which varied between 40 and 50 before and after transfusions. As shown by chart 2, there was no increase in output of bilirubin following the rapid fall in the hematocrit value. This was difficult to explain in view of the massive hemolysis which must have taken place. It may be that 1,300 to 1,400 mg. per day represents the maximum possible rate of production of bilirubin in this person.

CASE 2.—D. T., a 51 year old man of Italian extraction, was first seen in this clinic in 1933 because of blood-tinged sputum, which appeared during an attack of bronchitis. A roentgenologic examination of the chest, an examination of the sputum and a Wassermann test of the blood revealed nothing abnormal.

Five years later, in February 1939, he reappeared, complaining of shortness of breath of three months' duration. He felt that he had been losing strength for at least a year. He had not noted jaundice at any time, but the skin and scleras were found to be icteric. Dilated vessels of the face gave a ruddy appearance, but the mucous membranes and nail beds showed pronounced pallor. He was urged to enter the hospital, and finally did so three months later. Little further could be added to the history of his present illness. His dyspnea, pallor and jaundice had apparently been very insidious in onset and not accompanied by abdominal pain or change in the color of the urine.

He was born in Italy but had lived in San Francisco from the age of 2. No childhood diseases were recalled. Infections of the upper respiratory tract accompanied with bronchitis had been frequent during his adult life. He contracted a type of urethritis in 1933 which was said to be gonorrheal. Nocturia had been present for several years. Hernioplasties were done in 1912 and 1918. His consumption of alcohol had been moderate and consistent but had never interfered with good habits of eating. His father had died of cancer. There was no history of jaundice or anemia in parents or siblings.

Physical Examination.—Aside from the pallor of mucous membranes and nail beds and the icterus, the physical abnormalities observed were incidental. The

15. Castle, W. B., and Daland, G. A.: Susceptibility of Mammalian Erythrocytes to Hemolysis with Hypotonic Solutions, Arch. Int. Med. **60**:949 (Dec.) 1937.

skin showed no nevus araneus. The pupils were equal and reacted well to light and to the necessity for accommodation. Pyorrhea was present about carious teeth. Cervical and generalized adenopathy was absent. There were a few scattered wheezes and rhonchi heard over the chest. Cardiac enlargement was questionable. The rhythm was regular, and a soft systolic murmur was heard over the precordium. The blood pressure was 130 mm. of mercury systolic and 60 diastolic. The abdomen was obese, and the edge of the liver was felt below the costal margin, but the spleen was not palpable. No other masses were felt. There was a hydrocele on the left. The prostate was enlarged symmetrically and was moderately firm. The extremities were free of edema, and the deep tendon reflexes were equal and active. Position and vibratory sense were normal.

Laboratory Examination.—Examination of the blood gave the following values: hematocrit value, 13; erythrocytes, 1,090,000 per cubic millimeter; hemoglobin, 26 per cent Sahli (4.47 Gm. per hundred cubic centimeters); mean cell volume, 119 cubic microns; mean cell hemoglobin, 41 micromicrograms, and mean cell hemoglobin concentration, 34 per cent. Reticulocytes were 17 per cent, and there were about 250 normoblasts per cubic millimeter. The leukocyte count was 6,200, of which 76 per cent were polymorphonuclear leukocytes, 14 per cent lymphocytes and 10 per cent monocytes. Platelets numbered 250,000 per cubic millimeter. All specimens of serum examined were reported to show a slight hemoglobinemia, and the reaction to the direct Van den Bergh test was negative, to the indirect, 1.44 units. There was no increase in susceptibility of the red cells to hemolysis in hypotonic saline solution. The Donath-Landsteiner phenomenon could not be demonstrated, and tests for acid hemolysins were negative at this and at subsequent dates. Several preparations failed to demonstrate sickling.

His blood was found to be of group OMNRh +.

A biopsy of the bone marrow showed normoblastic hyperplasia.

Specimens of urine were of normal color and gave negative reactions to tests for protein and sugar, and the urine sediment contained nothing of significance. Stool specimens were free of gross and occult blood.

A determination of urea in the blood showed 45 mg. of urea per hundred cubic centimeters, and the total proteins in the blood were 6 Gm. per hundred cubic centimeters. Gastric analysis showed no free hydrochloric acid after the administration of histamine. Roentgenograms of the chest showed nothing abnormal.

Course.—There was little change during his stay of six weeks in the hospital. He remained afebrile and felt well while at rest. Hepatic extract given intramuscularly failed to increase reticulosis or to affect the hemoglobin level. There was no decrease in the signs of rapid destruction and regeneration of blood. He refused splenectomy and before discharge was given one transfusion of whole blood which produced a temporary rise in hemoglobin level.

During the next two years he was seen from time to time without change in blood values or in his symptoms and signs of his severe chronic hemolytic anemia.

Second Admission.—July 10, 1942: He was readmitted because of extreme dyspnea. The hemoglobin value was 21 per cent (3.6 Gm. per hundred cubic centimeters); there were 990,000 erythrocytes per cubic millimeter, and reticulocytes comprised 10 per cent of the red blood cells. Leukocyte counts were within normal range. On this admission the edge of the spleen was felt 2 cm. below the costal margin. There was definite cardiac enlargement. Two transfusions of whole blood raised the hemoglobin level to 38 per cent before the patient's discharge.

Third Admission.—Oct. 10, 1942: He was readmitted with a hemoglobin value of 26 per cent. Five transfusions of whole blood brought the hemoglobin level to 64 per cent, and he was discharged.

Fourth Admission.—March 17, 1943: This admission followed an attack of abdominal discomfort and an increase in icterus. He was afebrile, and leukocyte counts were normal. The spleen was felt as before. The hemoglobin value was 22 per cent, and the reaction to the indirect van den Bergh test was 7.4 units. He was again given a transfusion and discharged from the hospital.

	Peripheral Vein	Splenic Vein
Hematocrit value	46	44
Hemoglobin	82 per cent	80 per cent
Erythrocytes	4,400 per cubic millimeter	4,100 per cubic millimeter
Reticulocytes	3.6 per cent	3.8 per cent
Leukocytes	13,100	13,000
Platelets	169,300	166,800
Plasma	Hemoglobinemia +	Hemoglobinemia +
Mean corpuscular volume	104 cubic microns	107 cubic microns
Mean corpuscular diameter	8.86 microns	7.96 microns
Mean corpuscular thickness	1.8 microns	2.1 microns

Fragility in Hypotonic Saline Solution

	Hemolysis Begun	Hemolysis Definite	Hemolysis Intense	Hemolysis Complete
Blood from peripheral vein	0.50	0.42	0.38	0.28
Blood from splenic vein	0.54	0.46	0.40	0.30

Fifth Admission.—April 29, 1943: The hemoglobin level was 36 per cent, and the hematocrit value was 19. He was given two transfusions, totaling 500 cc. of concentrated red cells, without reaction, and the hematocrit value was raised to 25.

Sixth Admission.—May 19, 1943: His hematocrit value had dropped from 25 to 21 in nineteen days. After one transfusion of 500 cc. of concentrated cells he was discharged.

Seventh Admission.—July 27, 1943: During three weeks before admission he had become increasingly short of breath. He was icteric as usual, and the spleen and liver were palpable as before. The hematocrit value was 14, and the hemoglobin was 29 per cent. He was given 1,500 cc. of concentrated red cells in three procedures without reaction, which raised the hematocrit value to 36 and the hemoglobin to 78 per cent. The dyspnea was relieved.

Eighth Admission.—Oct. 6, 1943: The hematocrit value had fallen from 36 to 16 in two months' time, and his symptoms of severe anemia had returned. He at last consented to splenectomy, and, following repeated transfusions of concentrated red cells, splenectomy was performed on Oct. 9, 1943. During the procedure a sample of blood was withdrawn from the splenic vein. The results of examination of this sample are compared with those made on a sample taken from the antecubital vein at the same time.

His postoperative course was uneventful, and his icterus diminished gradually. He was discharged fifteen days after operation, only to be readmitted seven days later.

Ninth Admission.—Oct. 31, 1943: Three hours before admission he noted weakness of the right arm and leg and inability to coordinate his speech. There were definite motor weakness on the right and a mild degree of aphasia. His blood picture had changed very little, although the icterus index was still 15. Counts of blood platelets were 290,000 and 313,000 per cubic millimeter. He improved rapidly and was discharged at the end of nine days.

· During the ensuing months he was seen from time to time. There was a gradual fall in the hematocrit level at the rate of 1 to 1.5 mm. per month, and the icterus of the plasma became more pronounced.

On Oct. 5, 1944, a diet survey showed that he was consuming a diet high in fat, so that observations were begun while he was ambulatory after regulating his diet as to caloric intake and fat content. Results of these observations are presented in chart 4.

Tenth Admission.—Oct. 22, 1944: One year following splenectomy, when he was admitted for further observation, blood values were as follows: hematocrit value, 21.5; hemoglobin, 38 per cent (6.5 Gm. per hundred cubic centimeters),
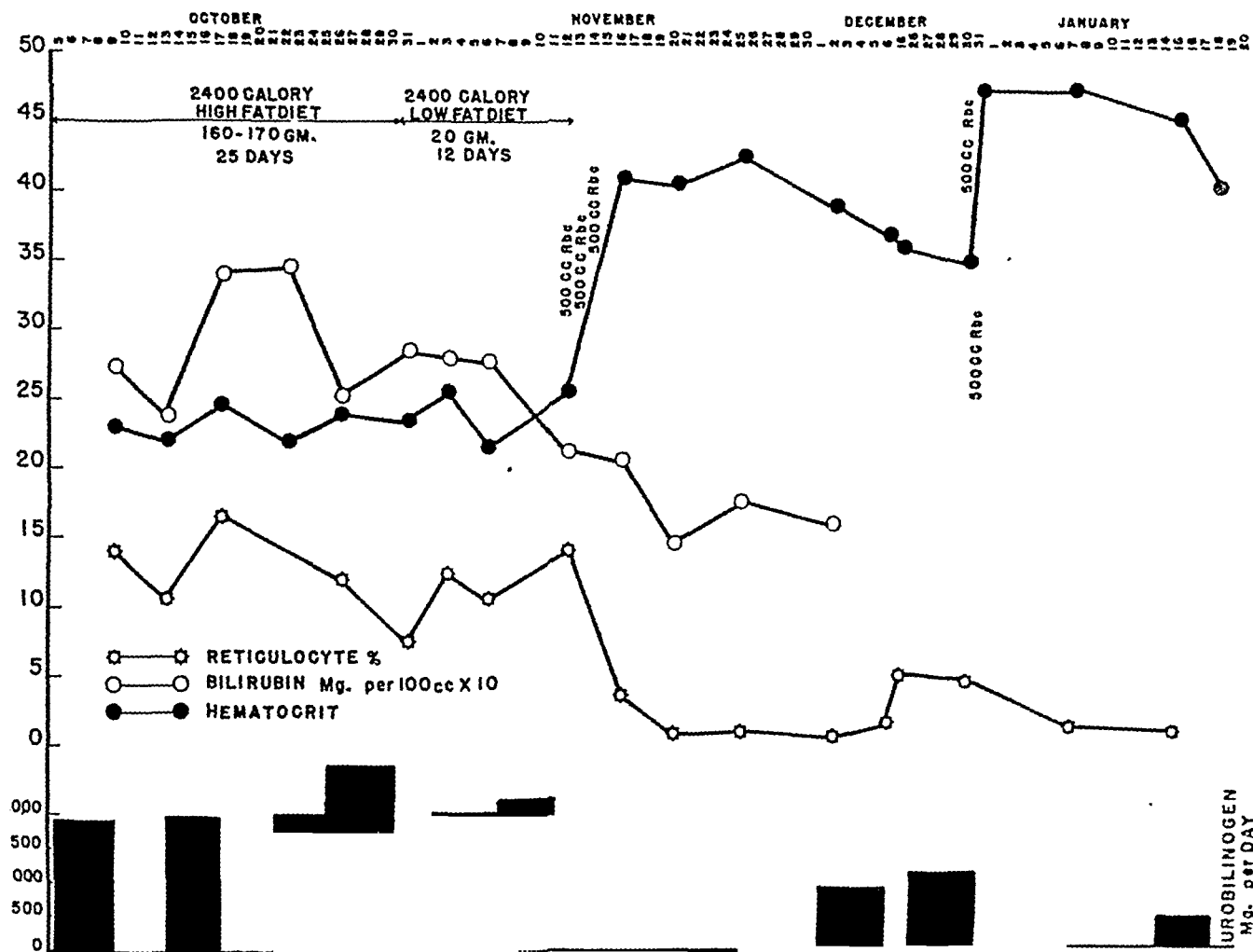
Chart 4.—Determinations of output of fecal urobilinogen of the patient who exhibited normal fragility of red blood cells in hypotonic saline solution and "pseudomacrocytosis" during periods of high and low intake of fat and following multiple transfusions.

and erythrocytes, 1,780,000 per cubic millimeter, with 30 per cent reticulocytes. Examination of the blood smear showed cells of normal and of greater than normal diameter exhibiting a normal pale center area. Few, if any, small densely staining cells lacking the pale central area were seen. The absence of spherocytes is evident from the Price-Jones curves, several of which fail to show any red blood cells of less than the normal range of diameter. The icterus index was 50, and the serum bilirubin was 3.4 mg. per hundred cubic centimeter. The leukocyte count was within normal range.

All his former symptoms of weakness and dyspnea on slight exertion had reappeared. No new physical abnormalities were evident. The blood pressure was 132 mm. of mercury systolic and 65 diastolic.

Course: He was continued on a diet high in fat for a period of nine days, making a total of twenty-four days, and then was given a diet low in fat for twelve days. Following this, 1,500 cc. of fresh concentrated red cells were given in three procedures, which raised the hematocrit value to 41, and he was discharged feeling greatly improved. He was able to return to work and was free of major symptoms for a period of forty-five days, when he was readmitted because of slight weakness; he felt that he would soon be incapacitated for moderately hard physical work.

Eleventh Admission.—Dec. 13, 1944: He was given 1,000 cc. of concentrated red cells in two procedures without reaction. The hematocrit value was raised from 35 to 48. He was discharged the day following entry feeling well and returned to work for six days. Then there developed an infection in the upper respiratory tract, for which he was seen and told to remain at home and in bed.

Twelfth Admission.—Jan. 18, 1945: On this date he experienced the onset of weakness of the right arm and inability to speak coherently. Physical examination showed weakness of the right hand and arm and motor aphasia. During the next few days the aphasia became complete, and he became weak and finally paralysis of the whole right side, including the face, set in. His temperature became elevated, and he sank into coma and died on the sixth day in the hospital.

Pathologic Examination: Spleen. The spleen weighed 400 Gm. The cut surface was smooth and firm, and there were no infarcts. The splenic pulp was congested and contained large numbers of reticuloendothelial cells, erythrocytes, macrophages and neutrophilic leukocytes. The reticuloendothelial cells contained phagocytized erythrocytes and hemosiderin granules.

Autopsy: The heart weighed 400 Gm., and none of the chambers was dilated. The coronary arteries were patent. There were red patches of consolidation in the lower lobe of the right lung. The peribronchial lymph nodes were not enlarged. No accessory spleen could be found. The liver weighed 2,200 Gm. and exhibited a smooth surface. A tiny fresh thrombus was found in one of the hepatic veins. The bile ducts and gallbladder were normal. Examination of the brain showed a small thrombus in the sagittal sinus. The entire left half of the cerebrum was soft and easily torn. The cerebral arteries were normal except for the left middle cerebral artery, which was distended by a reddish gray thrombus.

Microscopic examination showed slight intimal thickening of the left middle cerebral artery and no inflammation of the vessel around the fresh cellular thrombus. There was complete fresh necrosis of the left corpus striatum. The liver showed moderate atrophy of the central cells and dilatation of the sinusoids. Occasional tiny areas of focal necrosis were noted. Many of the small efferent veins contained fresh thrombi. There was little hemosiderin in the Kupffer cells. The kidney presented an unusual picture with large amounts of hemosiderin in the tubular epithelium. The epithelial cells were otherwise normal. The femoral marrow was hyperplastic, and phagocytosis of red cells was noted. There were large amounts of blood inside and outside the sinusoids, and leukoblastic elements were inconspicuous.

Experimental Data.—The Effects of High and Low Fat Diets: As stated previously, this patient had been consuming a diet which contained approximately 160 Gm. of fat daily. Observations which were begun while he continued with this regular diet at home are presented in chart 4. The diet high in fat was continued for eight days after he was admitted to the hospital, and he was then

changed to a diet low in fat, which was continued for twelve days. As can be seen from the chart, no significant change occurred in the hematocrit level, the reticulocyte count, the bilirubin in the blood or the output of urobilinogen in the feces during the course of the low fat intake. Perhaps twelve days is not sufficient time to give a conclusive answer, particularly in view of the somewhat lowered level of bilirubin in the blood at the termination of the observations, but it was not possible to extend the period of observation. He was therefore returned to a regular diet, and multiple transfusions were begun.

The Effect of Red Cell Transfusions: He was given transfusions of 500 cc. of concentrated red cells on three successive days, which raised the hematocrit level from 24 to 41 and the hemoglobin to 13 Gm. per hundred cubic centimeters. The percentage of reticulocytes fell to a normal range following the pronounced increase in the circulating hemoglobin. The bilirubin in the blood remained at a lower level after transfusions. The sudden decrease in daily output of urobilinogen in the stool is shown by the measurements made beginning five days following the last transfusion. The output of urobilinogen, which had been 2,000 mg. daily or higher, suddenly fell to 700 mg. per day. During the next forty-five days the hemotocrit value fell slowly to a level of 35, the percentage of reticulocytes remained at the level of 1 or 2 for most of that time, and the excretion of urobilinogen, while considerably above normal, was roughly half the previous amount.

It was intended that the excretion of urobilinogen could be followed as the anemia became more severe and regeneration of blood became more rapid, but the patient felt that he must remain at work; hence he was given two transfusions of concentrated cells, which raised the hematocrit value to 48, in the hope that the formation of blood would be completely inhibited for a time. A determination of urobilinogen excretion begun three days later showed no decrease in output. However, the last determination, completed at the time of onset of the cerebral thrombosis and hemorrhage, showed an excretion of less than 500 mg. daily. Since he was suffering from a respiratory infection at the time and accompanying disturbance of bowel activity, it may be doubted that this was a complete collection, even though the patient insisted that it was.

COMMENT

There can be no doubt that the chronic anemia in both patients was maintained by an accelerated rate of destruction of erythrocytes. Destruction of blood as measured by the excretion of bilirubin and urobilinogen, has been shown to be many times normal. Rapid formation of blood, indicated by 10 to 30 per cent reticulocytes in the circulating blood, has been constantly in evidence throughout several years of observation. The hemolytic anemia developed during adult life in both patients, and in neither case is there evidence in the past history to suggest a previous hemolytic disorder. The patient whose cells exhibit spherocytosis has 2 daughters whose erythocytes show a normal resistance to hemolysis in hypotonic saline solution. In both patients the hemolytic process developed insidiously and was manifested by the gradual development of symptoms referable to the anemia. No change of living habits or state of health preceded the onset of the disease in the man. The other patient was receiving gold therapy for

arthritis at the time that her hemoglobin and erythrocyte count began to fall. Chart 1 shows a steady drop in hemoglobin to the point where jaundice, splenomegaly and reticulosis gave convincing evidence that the anemia was hemolytic in origin. Disorders of hemopoiesis, namely aplastic anemia, granulocytopenia, and thrombopenic purpura, have all been observed after the use of gold therapy,[16] but I have been unable to find a report that hemolytic anemia has resulted from its use. It is difficult to believe, however, that the administration of a gold preparation and the onset of accelerated destruction of the blood were purely coincidental. On the other hand, if gold therapy was instrumental in initiating the process it is not explained why it increased in severity and became chronic long after the injections of the gold preparation were discontinued, since hemolytic anemias due to lytic substances or to hypersensitivity usually subside after the removal of the causative agent.

There is good evidence that the splenectomy had a distinctly beneficial although largely temporary effect for both patients. The first patient had a spontaneous rise in hemoglobin from 38 to 65 per cent during the first few days following splenectomy. However, three months later the hemoglobin was found to be close to the level prevailing before the splenectomy. It could be argued that splenectomy had some lasting benefit, since the anemia was evidently gradually increasing in severity at the time the spleen was removed. There is of course no proof that it had not reached its lowest point and become stabilized just prior to splenectomy. The second patient underwent splenectomy after the hematocrit value had been restored to normal by transfusions of red cells. However, the rate of fall of the hematocrit value following splenectomy was much slower than it had been following previous transfusions of red cells. Prior to the splenectomy the hematocrit level had dropped from a normal range to the level before transfusion within two months' time. Following splenectomy the fall was so gradual that a year elapsed before the anemia approached the former severe degree. It should be noted that during the period of study the anemia of this patient did not reach the degree of severity that was usual before splenectomy, when the hematocrit value was frequently as low as 16.

The reason that splenectomy was followed by a temporary and partial remission in the hemolytic process is not clear. The studies made of the specimen of blood withdrawn from the splenic vein of our second patient at the time of operation yielded no information which seems of crucial value. All measurements indicate that the average erythrocyte was a little greater in volume and had a slightly smaller diameter and was therefore somewhat thicker than the average erythro-

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16. Lintz, R. M.: Toxic Reactions with Gold Salts in Treatment of Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:1629 (July) 1941.

cyte in a peripheral vein. The demonstrable difference in fragility in hypotonic saline solution is a reflection of the increase in mean cell thickness. However, recent studies of blood from a splenic vein in a variety of conditions indicate that these differences, which are slight, are probably within the limits of the normal.[17]

The descriptions of the histopathologic condition of the spleen removed from our patients are also of little aid in postulating the role each organ played in the accelerated destruction of erythrocytes. There is no histologic evidence that their activity was essentially different in the 2 cases. Indeed the similarity of the histologic picture and the partial response to splenectomy indicate that the spleens had a partial or secondary role in destruction of the blood rather than a primary one.

It has not been possible to demonstrate the presence of isohemolysin or isoagglutinin in the blood of either patient by tests in vitro. However, from the studies made following transfusions there is good evidence that in the patient with spherocytosis a potent agent is present which changes the shape and increases the fragility of the transfused cells in hypotonic saline solution overnight. It was also demonstrated that there was a rapid return of the anemic state following transfusion, which must have been due to hemolysis of the transfused cells as well as of the patient's cells.

The hemolytic agent could not be demonstrated in vitro by studies designed to measure the same action it was shown to have in vivo, namely, the effect on the shape and structure of normal cells and on their fragility in hypotonic saline solution. Its nature therefore is not known, but presumably it is the same agent that acts on the patient's erythrocytes. Since it is not easily demonstrable in the peripheral blood there is less difficulty in supposing it to be an immune body type of hemolysin than a simple lytic substance. The supply of the substance is evidently great, however, since the development of spherocytosis and subsequent hemolysis was as rapid after the second transfusion of 1,000 cc. of red cells as after the first, a week previously. These observations confirm the statement of Rous [18] that a hemolytic substance which may not be demonstrable in vitro may produce damage in vivo.

As stated previously, the erythrocytes of the first patient have always shown a tendency toward diminished cell diameter and increased cell thickness. The reasons that erythrocytes lose their bilaterally

17. Watson, C. J., and Paine, J. R.: A Study of the Splenic Venous Blood with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes Before and After Splenic Arterial Injection of Adrenalin, Am. J. M. Sc. **205**:493 (April) 1943.

18. Rous, P.: The Destruction of Red Blood Corpuscles in Health and Disease, Physiol. Rev. **3**:75 (Jan.) 1923.

concave form and become spherocytic are evidently various.[19]   It seems probable that the fundamental change is the absorption of fluid and a consequent increase in cell volume.   An increase in cell volume has been noted to accompany the development of spherocytosis in stored blood,[20] and Dameshek and Schwartz [21] found evidence of an increase in cell volume concomitant with the development of spherocytosis in experimental hemolytic anemia.   In our patient with spherocytosis data have been presented which indicate that following multiple transfusions of red cells a significant increase in mean cell volume occurred along with the development of spherocytosis and increased fragility in hypotonic saline solution.   Since an increase in volume through the absorption of fluid would account for the changes in cell morphology observed, it seems likely that the primary effect of the *lytic substance was damage to the cell which caused or permitted the* absorption of fluid.

While spherocytosis is not a constant feature of hemolytic phenomena, when it is present the factor of increased mechanical fragility is doubtless of considerable importance in accelerating the rate of hemolysis.   Shen, Castle and Fleming [22] demonstrated that spherocytic cells exhibit an increased mechanical fragility when rotated with glass beads. They stated their belief that the spherocyte is less able to withstand the changes in shape involved in capillary circulation than is the normal erythrocyte.   The mechanical fragility of the cells of our patient with spherocytosis was roughly twelve times normal, while the cells of the second patient *without spherocytosis showed a normal mechanical* fragility.   It is reasonable to suppose, therefore, that hemolysins which produce spherocytosis of erythrocytes accelerate the rate of destruction of blood by increasing the mechanical fragility or by causing further absorption of fluid to the point where rupture of the cell membrane or diffusion of hemoglobin from the cell occurs.

The second patient has never shown spherocytosis or increased fragility of cells in hypotonic saline solution but has always presented a moderate macrocytosis.   A macrocytic blood picture has been frequently described in acquired hemolytic anemia and is due to the presence of large numbers of reticulocytes, which always tend to be

19. Dameshek, W., and Miller, E. B.:   Pathogenic Mechanisms in Hemolytic Anemias, Arch. Int. Med. **72**:1 (July) 1943.

20. Crosbie, A., and Scarborough, H.:   Studies on Stored Blood: VI. Changes in the Erythrocytes During Storage, Edinburgh M. J. **48**:253 (April) 1941.

21. Dameshek, W., and Schwartz, S. O.:   Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, Am. J. M. Sc. **196**:769 (Dec.) 1938.

22. Shen, S. C.; Castle, W. B., and Fleming, E. M.:   Experimental and Clinical Observations on Increased Mechanical Fragility of Erythrocytes, Science **100**:387 (Oct. 27) 1944.

larger than the mature cells. It seems clear from chart 4 that the transfused erythrocytes were not destroyed with great rapidity in this patient, since it required forty-five days for the hematocrit value to drop from 40 to 35. There is also evidence of a slower rate of destruction of blood following transfusion as shown by the diminished daily output of urobilinogen which occurred in spite of the increase in red cell volume. Josephs [23] has shown that the rate of destruction of blood may decrease sharply following the transfusion of whole blood or plasma in certain types of hemolytic anemia. Since the concentrated red cells used are suspended in approximately 10 per cent plasma it is possible that the diminished hemolysis was due to an antihemolytic substance in normal plasma. Because of the patient's death this possibility was not investigated. However, prior to splenectomy there is no evidence that transfusions of whole blood produced a partial remission in the hemolytic process.

A second possible explanation of the diminished hemolysis should be considered, particularly since the partial remission was so prolonged. The fall in output of urobilinogen followed closely the drop in the percentage of reticulocytes to a normal range. Since the rate of destruction of blood seems so closely related to the rate of formation of blood, it seems possible that the newly formed cell or reticulocyte may have been the most vulnerable to hemolysis. If this suggestion is correct the mechanism of the hemolysis is not explained, but it seems more likely that the defect would lie in cell structure rather than in the selective action of a hemolytic agent. However, it is evident that even when formation of blood was close to normal the excretion of urobilinogen was still several times the normal value, so that it is probable that mature cells were also being destroyed. There is no evidence that the spleen played a part in the hemolysis of young erythrocytes, since the percentage of reticulocytes in the blood from the splenic vein was the same as that in the blood from the peripheral vein. No attempt was made to determine the rate of destruction of the transfused cells as compared to that of the patient's cells; hence no data are at hand to estimate what proportion of the excretion of urobilinogen following transfusion was contributed by the transfused cells.

There seems to be little precedent for the postulate that the immature erythrocytes may be the most susceptible to hemolysis in certain cases of hemolytic anemia, but it is offered as a plausible possibility for further investigation. The reticulocyte has been shown to possess

23. Josephs, H. W.: Studies in Haemolytic Anaemia: II. The Presence of an Anti-Hemolytic Factor in Human Plasma, Bull. Johns Hopkins Hosp. 62:53 (Jan.) 1938.

certain physical characteristics, aside from the inclusion of a basophilic substance, which differ from those of the mature erythrocyte. In addition to its greater size the reticulocyte has been reported to be more adhesive than the mature cells.[24]   Kitchen [25] has demonstrated that it is more susceptible to invasion by Plasmodium vivax than are mature erythrocytes, and Dock and Mermod [26] have presented evidence to show that the serum of patients with untreated pernicious anemia has a selective lytic action for reticulocytes in vitro and that saponin has a selective lytic action on reticulocytes in vivo in rabbits.[27]

The death of our second patient brought to an end observations which might have thrown further light on the relationship of the rate of hemolysis to that of formation of blood and to transfusions of whole blood and plasma. The cause of the cerebral thrombosis is not clear, as no underlying disease of the arterial system was demonstrated. A previous cerebral vascular accident following splenectomy and involving the same area was equally unexplained, since it was not associated with an elevated platelet count or evidence of embolism. It seems possible that the increase in viscosity of the blood following the elevation of the hematocrit value to 48 and the increase of plasma fibrinogen which may have attended the respiratory infection predisposed to a thrombosis which might not otherwise have occurred.

From the data accumulated there is no evidence that the fat content of the diet had any effect on the rate of hemolysis which might be considered important from a therapeutic standpoint. In retrospect the periods of observation seem rather brief, particularly with regard to the second patient, who was changed from a diet high in fat to one low in fat. However, after the transfusions he returned to his normal diet, which was high in fat content, and yet exhibited a reduced output of urobilinogen for a long period of time.

SUMMARY AND CONCLUSIONS

The histories of 2 patients with chronic hemolytic anemias have been presented. One patient has always exhibited spherocytosis and an increased fragility of red blood cells in hypotonic saline solution. The onset of the disease in her case followed the therapeutic injection

24. Davidson, L. S. P.: The Basophilic Substance of the Erythrocyte, Edinburgh M. J. **37**:425 (Aug.) 1930.

25. Kitchen, S. F.: The Infection of Reticulocytes by Plasmodium Vivax, Am. J. Trop. Med. **18**:347 (July) 1938.

26. Dock, W., and Mermod, C.: Hemolysins to Which Reticulocytes Are Especially Vulnerable in the Plasma of Primary Anemia, Proc. Soc. Exper. Biol. & Med. **32**:373 (Nov.) 1934.

27. Mermod, C., and Dock, W.: Fragility and Maturation of Reticulocytes, Arch. Int. Med. **55**:52 (Jan.) 1935.

of colloidal gold for arthritis. No hemolytic agent could be demonstrated by tests in vitro, but after a massive transfusion of red cells it has been shown that transfused erythrocytes acquire an increased fragility in hypotonic saline solution within twenty-four hours after injection. This change is accompanied by an increase in mean cell volume and a decrease in mean cell diameter. It seems likely that the lytic substance produces these changes by damaging the cell so as to cause absorption of fluid.

The second patient described has never exhibited spherocytic erythrocytes, and the fragility of red blood cells in hypotonic saline solution has always been normal. Restoration of the circulating hemoglobin to a normal level by multiple transfusions of red blood cells was followed by evidence of diminished hemolysis. While this effect might have been due to an antihemolytic factor in human plasma, the suggestion is made that, since the amount of output of pigment is so closely associated with formation of blood, it was the reticulocytes, or newly formed cells, which were the most susceptible to hemolysis in this patient. This suggests that the defect was inherent in the patient's erythrocytes, although other possibilities must be considered.

No information was gained from either patient to indicate that the fat content of the diet was of therapeutic importance in the rate of blood destruction. Of some therapeutic significance is the fact that 1 patient was not benefited by multiple transfusions while the other was able to return to work and exhibited a diminished rate of blood destruction following the restoration of the circulating hemoglobin to normal level.

CONCENTRATED HUMAN ALBUMIN IN THE TREATMENT OF SHOCK

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WHOLE blood is the best replacement fluid for treating patients with acute hemorrhage. It has the disadvantage of being difficult to preserve and bulky to transport, and it must be typed before it is administered. In an effort to overcome these difficulties plasma has been used extensively. It has the advantage that it can be given without typing. However, it is bulky to transport in liquid or frozen state, and it is easily contaminated by bacteria. When dried, plasma is stable, but time must be taken to restore it to liquid state. A substitute for plasma which could be packaged in concentrated form, which did not need to be preserved by drying or freezing, which was stable under all types of motion produced by ships or tanks and which could be given rapidly in large quantities without reaction was obviously needed. On theoretic grounds the solution of concentrated human albumin made possible by the work of Cohn and his colleagues at Harvard University appeared to be the ideal substitute for plasma.[1]

A test of the usefulness of human albumin[2] as a substitute for plasma has been made at Grady Hospital by observing the effects of giving it intravenously to 7 normal subjects and to 34 patients with circulatory failure.

1. Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., Jr., and Armstrong, S. H., Jr.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: I. The Characterization of the Protein Fractions of Human Plasma, J. Clin. Investigation 23:417, 1944.

2. The products of plasma fractionation employed in this work were developed from blood, collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

METHODS

The technics used in this study have been described in detail elsewhere.[3] A catheter was introduced into the right atrium by way of the antecubital vein to obtain samples of mixed venous blood and to measure the mean atrial pressure in millimeters of water. The consumption of oxygen was measured by analyzing a two minute sample of expired air collected in a Douglas bag. Samples of arterial blood and optical recording of arterial pressure were obtained by placing an inlying needle in the femoral artery. The oxygen content of the arterial and right atrial blood was determined by the method of Van Slyke.[4] The cardiac output was calculated by the utilization of the Fick principle. A point 5 cm. posterior to the fourth costochondral junction was taken as the zero point for calculating the right atrial pressure. The plasma volume was measured by injecting the blue dye T-1824 (Evans' blue) and determining its concentration either in a series of samples or in a single sample collected ten minutes after the dye was injected. If there was no evidence of further bleeding, the change in blood volume after therapy was usually estimated from the change in the hematocrit reading. Heparin was used as the anticoagulant in the hematocrit tubes. The concentration of protein was measured by the falling drop method. Since the output of the heart varies with the size of the person, the cardiac indexes rather than the output are frequently referred to in this paper. The cardiac index is the cardiac output measured in liters of blood per minute per square meter of body surface.

RESULTS

No untoward effects were noted. None of the patients experienced chills, fever, urticaria, pulmonary edema or circulatory collapse.

NORMAL SUBJECTS

Seven normal subjects received 1 liter of a 5 per cent solution of human albumin intravenously (see table). The time required for the infusion ranged from fifteen to thirty-one minutes. Two consistent changes were noted. The atrial pressure always rose, and the hematocrit reading and concentration of hemoglobin always fell. The arterial pressure, cardiac rate, consumption of oxygen and arteriovenous oxygen difference showed no consistent change. The cardiac output

3. Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization: Normal Values with Observations on the Effect of Anxiety and Tilting, J. Clin. Investigation **24**:326, 1945.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

Patient	Diagnosis	Age	Sex	Surface Area, Sq. M.	Oxygen Consumption, Cc. per Min. per Sq. M.	Oxygen Saturation of Arterial Blood, per Cent	Arterial Oxygen Content, Vol. per Cent	Mixed Venous Oxygen Content, Vol. per Cent
	Normal Subjects							
L. R.	Control	22	M	1.95	116	..	18.2	14.9
	Immediately after albumin*..............................				108	..	15.4	11.9
	70 minutes after albumin.................................				133	..	16.0	12.7
C. P.	Control	32	M	1.69	151	..	16.4	12.9
	Immediately after albumin...............................				170	..	15.2	11.5
F. L.	Control	41	F	1.61	117	..	13.8	10.4
	10 minutes after albumin.................................				119	..	10.9	7.9
	55 minutes after albumin.................................				137	..	11.0	8.0
J. B.	Control	36	M	2.0	127	..	17.4	13.8
	55 minutes after albumin................... .				111	..	14.8	12.3
L. L.	Control	16	M	1.73	142	..	17.0	11.4
	Immediately after albumin...............................				130	..	14.4	10.5
	60 minutes after albumin.................................				124	..	15.8	11.8
W. W.	Control	57	M	1.73	129	..	16.0	11.8
	Immediately after albumin...............................				121	..	13.0	10.6
	60 minutes after albumin.................................				120	..	13.3	11.0
A. W.	Control	33	M	1.74	120	..	12.2	9.6
	Immediately after albumin...............................				127	..	10.1	5.2
	100 minutes after albumin................................				118	..	....	....
	Patients with Hemorrhage							
C. R.	Bleeding peptic ulcer......................	56	M	2.09	...	..	....	....
	Immediately after 25 Gm. albumin‡......................				...	..	....	....
	30 minutes after albumin.................................				...	..	....	....
A. D.	Lacerations	33	F	1.64	112	..	11.9	5.8
	20 minutes after 50 Gm. albumin........................				...	..	....	....
	60 minutes after albumin.................................				113	..	9.2	6.2
L. D.	Lacerations	26	M	1.60	136	..	16.7	11.9
	Immediately after 50 Gm. albumin......................				...	..	....	....
	30 minutes after albumin.................................				157	..	13.8	10.4
C. J.	Lacerations	39	M	1.76	127	..	14.9	6.8
	Immediately after 50 Gm. albumin......................				...	..	....	....
	30 minutes after albumin.................................				142	..	12.4	7.7
L. A.	Lacerations	15	M	1.68	113	..	13.1	8.1
	Immediately after 50 Gm. albumin......................				...	..	....	....
	30 minutes after albumin.................................				126	..	11.8	8.2
	5 minutes after 500 cc. saline...........................				126	..	10.9	8.0
A. L. C.	Lacerations	21	M	1.92	...	..	....	....
	35 minutes after 50 Gm. albumin........................				...	..	....	....
F. G.	Lacerations	25	F	1.75	...	..	....	....
	Immediately after 50 Gm. albumin...................... .				...	..	....	....
	15 minutes after albumin.................................				...	..	....	....
W. B.	Lacerations	30	M	1.80	...	..	....	....
	Immediately after 50 Gm. albumin......................				...	..	....	....
	20 minutes after albumin.................................				...	..	....	....
H. F.	Lacerations	45	M	1.68	116	..	14.5	10.7
	Immediately after 50 Gm. albumin......................				...	..	12.6	10.0
	25 minutes after albumin.................................				...	..	....	....
H. W.	Lacerations	33	M	1.80	...	..	....	....
	Immediately after 50 Gm. albumin......................				...	..	....	....
	60 minutes after albumin.................................				...	..	....	....
T. A.	Lacerations	30	M	2.0	...	..	....	....
	Immediately after 50 Gm. albumin......................				...	..	....	....
	60 minutes after albumin.................................				...	..	....	....
M. Z.	Lacerations	22	F	1.46	111	..	11.9	6.8
	20 minutes after 50 Gm. albumin........................				145	..	10.4	7.4
J. H.	Lacerations	34	M	1.72	...	.:	....	....
	Immediately after 50 Gm. albumin......................				...	..	....	....
	30 minutes after albumin.................................				...	..	....	....

Arterio-venous Oxygen Difference, Vol. per Cent	Cardiac Output, Liters per Min.	Cardiac Index, Liters per Min. per Sq. M.	Hemoglobin, Gm. per 100 Cc.	Hematocrit Reading	Systolic Pressure, Mm. of Hg	Diastolic Pressure, Mm. of Hg	Mean, Mm. of Hg	Pulse Rate, Beats per Min.	Peripheral Resistance, Absolute Units	Total Plasma Protein, Gm. per 100 Cc.	Atrial Pressure, Mm. Water	Blood Volume, Cc. per Sq. M.	Increase in Blood Volume, Cc. per Gm. Albumin	Blood Alcohol, Mg. per 100 Cc.	Additional Fluids Given, Cc. Saline Solution
Normal Subjects															
3.3	6.9	3.5	14.5	41	127	69	91	65	1,050	6.0	40	.....	..	..	...
3.5	6.0	3.0	12.2	36	120	68	87	73	1,200	5.7	110	.....	..	..	...
3.3	7.8	4.0	12.7	39	...	..	..	..	.....	5.9	75	.....	..	..	...
3.5	7.3	4.3	....	45	110	65	81	100	880	5.9	15	.....	..	..	...
3.7	7.8	4.6	....	37	113	65	80	103	820	5.6	120	.....	..	..	...
3.4	5.5	3.4	10.0	34	136	78	98	94	1,420	7.2	—15	.....	..	..	...
3.0	6.3	3.9	8.8	27	127	72	92	94	1,170	6.7	45	.....	..	..	...
3.0	7.5	4.6	8.9	28	140	80	100	84	1,060	6.8	15	.....	..	..	...
3.6	7.1	3.6	14.2	46	125	75	88	88	1,000	6.8	—15	.....	..	..	...
2.5	8.7	4.4	12.6	39	155	79	103	60	950	6.5	30†	.....	..	..	...
5.6	4.4	2.5	14.8	43	119	68	83	53	1,510	5.5	60	2,560	..	..	...
3.9	5.7	3.3	11.5	33	142	78	99	60	1,390	5.0	190	3,280	..	..	...
4.0	5.4	3.1	13.8	37	142	78	98	52	1,450	5.6	90	2,980	..	..	...
4.2	5.3	3.1	12.7	38	163	86	113	66	1,700	5.9	20	2,600	..	..	...
2.4	8.8	5.1	10.0	29	166	84	113	66	1,030	5.5	90	3,360	..	..	...
2.3	9.0	5.2	10.4	32	150	77	105	60	930	5.8	50	3,050	..	..	...
2.6	8.1	4.6	9.5	32	107	47	66	60	660	6.1	5	.....	..	..	...
4.9	4.5	2.6	8.1	27	107	47	69	71	1,220	6.2	105	.....	..	..	...
...	...	...	7.8	..	...	..	..	..	.....	6.4	45	.....	..	..	...
Patients with Hemorrhage															
...	...	...	....	22	120†	58	..	90	.....	4.4	...	1,900	..	..	...
...	...	...	....	..	108†	46	..	90	.....	...	...	.....	..	..	...
...	...	...	....	19	104†	56	..	84	.....	4.5	...	2,210	27	..	...
6.1	2.9	1.8	9.8	33	68	43	53	107	1,490	5.4	5	.....	..	180	...
...	...	...	7.8	26	98	60	72	100	.....	6.1	40	.....	..	..	...
3.0	6.2	3.8	7.3	24	102	59	75	100	960	5.6	40	.....	..	..	200
4.8	4.5	2.8	12.7	38	91	65	69	96	1,230	5.6	15	2,310	..	348	...
...	...	...	11.4	32	142	83	104	100	.....	6.2	85	2,880	18	..	180
3.4	7.6	4.8	10.8	31	139	77	100	96	1,050	5.9	85	2,940	..	..	...
8.1	2.8	1.6	12.1	36	61	33	41	80	1,160	5.4	10	.....	..	..	...
...	...	...	10.0	32	...	..	..	..	.....	6.0	30	.....	..	..	...
4.7	5.3	3.0	10.0	31	75†	50	..	67	.....	5.8	55	.....	..	..	300
5.0	3.8	2.3	10.1	33	89	58	70	88	1,470	4.9	0	2,020	..	..	...
...	...	...	....	31	...	..	..	..	.....	6.0	50	2,320	..	..	...
3.6	5.9	3.5	8.8	29	107	61	76	79	1,070	5.6	20	2,440	10	..	150
2.9	7.3	4.3	8.2	27	124	65	85	79	930	5.0	70	2,620	14	..	500
...	...	...	....	42	80†	60	..	100	.....	5.4	...	2,450	..	..	....
...	...	...	....	39	127†	74	..	96	.....	6.2	...	2,600	6	..	....
...	...	...	....	35	88†	48	..	110	.....	5.1	...	1,800	..	219	....
...	...	...	....	..	110†	64	..	106	.....	...	...	.....	..	..	....
...	...	...	....	30	...	..	..	..	.....	5.6	...	2,080	10	..	....
...	...	...	....	40	80†	54	..	68	.....	5.0	...	2,890	..	..	....
...	...	...	....	..	112†	74	..	72	.....	...	...	3,270	17	..	...
...	...	...	....	34	116†	66	..	66	.....	5.2	...	2,320	..	180	...
3.8	5.1	3.1	11.1	36	90	56	68	88	1,070	5.6	20	2,670	12	..	...
2.6	...	...	9.7	31	110	62	81	100	.....	5.6	60	2,800	16	..	300
...	...	...	....	30	...	..	..	..	.....	...	...	.....	..	..	...
...	...	...	....	35	47	28	37	99	.....	....	...	.....	..	62	...
...	...	...	....	32	88	52	61	114	.....	...	...	.....	..	..	...
...	...	...	....	30	84	48	59	84	.....	...	...	.....	..	..	...
...	...	...	....	40	86	54	68	96	.....	...	...	2,630	..	169	...
...	...	...	....	35	106	60	79	96	.....	...	...	2,960	13	..	...
...	...	...	....	34	110	64	80	96	.....	...	...	3,050	17	..	...
5.1	3.2	2.2	10.2	32	86	47	59	72	1,480	5.8	5	1,820	..	..	125
3.0	7.0	4.8	7.8	25	130	75	98	96	1,120	6.5	45	2,300	14	..	...
...	...	..	....	47	92†	66	..	108	.....	6.1	...	1,980	..	314	...
...	...	...	....	42	88†	66	..	104	.....	6.7	...	2,200	8	..	...
...	...	...	....	40	106†	72	..	106	.....	6.7	...	2,310	12	..	...

Patient	Diagnosis	Age	Sex	Surface Area, Sq. M.	Oxygen Consumption, Cc. per Min. per Sq. M.	Oxygen Saturation of Arterial Blood, per Cent	Arterial Oxygen Content, Vol. per Cent	Mixed Venous Oxygen Content, Vol. per Cent
	Patients with Injuries of Chest							
L. D.	Stabbed chest §	27	M	1.65	167	..	14.7	10.9
	Immediately after 50 Gm. albumin				...	..	....	....
	38 minutes after albumin				167	..	14.1	10.9
O. M.	Stabbed chest	20	F	1.46	122	..	9.4	5.7
	25 minutes after 50 Gm. albumin				123	..	7.4	4.2
W. W.	Stabbed chest	33	M	1.83	192	..	16.2	10.6
	12 minutes after 50 Gm. albumin				189	..	16.5	11.6
	35 minutes after albumin				...	..	....	....
A. E.	Fractured ribs	71	F	1.57	104	67	8.2	2.6
	5 minutes after 25 Gm. albumin				...	..	7.4	2.2
	10 days later				138	92	11.5	6.9
W. L. T.	Stabbed chest	52	M	1.87	107	..	13.6	9.4
	35 minutes after 50 Gm. albumin				107	..	12.1	8.4
P. D.	Stabbed chest	34	M	1.67	151	88	15.0	10.1
	5 minutes after 50 Gm. albumin				183	..	13.2	9.1
V. S.	Stabbed chest	23	F	1.76	...	..	....	....
	Immediately after 50 Gm. albumin				...	..	....	....
	30 minutes after albumin				...	..	....	....
	Patients with Stabbed Heart							
N. B.	Before therapy	39	M	1.72	180	..	12.8	7.0
	Immediately after 25 Gm. albumin in 500 cc. saline sol				179	..	11.7	6.9
	68 minutes after albumin				...	..	....	....
S. W.	Before therapy	32	M	1.80	111	..	16.2	10.4
	Immediately after 50 Gm. albumin				109	..	14.1	9.4
	Patients with Miscellaneous Conditions							
A. W.	Dehydration—ileostomy	34	F	1.32	116	..	12.2	9.4
	3 hours after 50 Gm. albumin and 1,500 cc. saline sol				164	..	8.8	6.8
W. G.	Extensive burns	58	F	1.60	141	..	16.1	10.9
	After 500 cc. saline sol				113	..	15.7	9.8
	After 3,000 cc. saline sol and dextrose				112	..	15.6	10.5
	After 50 Gm. albumin				160	..	13.2	8.9
B. L.	Extensive burns	80	..	1.2	103	..	18.2	8.8
	25 minutes after 50 Gm. albumin				133	..	15.2	8.9
W. J.	Extensive burns	..	..	1.52	172	..	17.5	13.5
	43 minutes after 50 Gm. albumin				238	..	16.6	12.4
	2 hours later				173	..	15.3	13.4
RM. H.	Reaction to oxophenarsine hydrochloride	16	F	1.92	176	..	18.1	9.6
	Immediately after 50 Gm. albumin				...	..	....	....
	Immediately after 25 Gm. albumin				...	..	....	....
	37 minutes after albumin				180	..	17.0	10.0
T. F.	Pneumonia	31	M	1.81	210	..	19.3	5.0
	12 minutes after 75 Gm. albumin				329	..	16.2	9.2
	Immediately after 850 cc. saline sol				350	..	15.6	9.2
M. B.	Pneumonia	30	F	1.41	149	..	17.5	13.5
	Immediately after 25 Gm. albumin and 1,000 cc. saline sol.				145	..	14.8	10.7
F. S.	Acute peritonitis	39	M	2.08	136	..	17.9	11.6
	5 minutes after 75 Gm. albumin				118	..	15.8	12.1
	40 minutes after albumin				...	..	....	....
S. K.	Periurethral abscess—drained	39	M	1.91	143	..	12.3	5.8
	Immediately after 75 Gm. albumin				147	..	9.3	5.5
E. J.	After nephrectomy for tuberculous kidney	30	F	1.31	116	..	15.6	10.0
	5 minutes after 50 Gm. albumin				118	..	12.9	8.6
W. H.	After operation for gunshot wound in abdomen	44	M	1.97	205	..	17.8	7.4
	5 minutes after 75 Gm. albumin				236	..	14.4	9.1

* All normal subjects received 1,000 cc. containing 50 Gm. of human serum albumin in isotonic solution of sodium chloride.

† By auscultatory methods.

‡ All patients received 25 per cent human serum albumin unless otherwise stated.

§ All initial studies were made prior to albumin therapy.

Arterio-venous Oxygen Difference, Vol. per Cent	Cardiac Output, Liters per Min.	Cardiac Index, Liters per Min. per Sq. M.	Hemoglobin, Gm. per 100 Cc.	Hematocrit Reading	Systolic Pressure Mm. of Hg	Diastolic Pressure Mm. of Hg	Mean, Mm. of Hg	Pulse Rate, Beats per Min.	Peripheral Resistance Absolute Units	Total Plasma Protein, Gm. per 100 Cc.	Atrial Pressure, Mm. Water	Blood Volume, Cc. per Sq. M.	Increase in Blood Volume, Cc. per Gm. Albumin	Blood Alcohol, Mg. per 100 Cc.	Additional Fluids Given, Cc. Saline Solution
Patients with Injuries of Chest
3.8	7.2	4.4	12.5	42	88	56	66	88	730	5.8	20	.....	..	155	359
...	...	...	11.3	38	130	82	95	112	.....	6.5	50	.....	12	..	...
3.2	8.6	5.2	10.9	37	120	72	88	108	820	6.2	50	.....	..	..	...
3.7	4.8	3.3	8.2	26	80	48	62	68	1,030	5.6	5	1,770	..	..	...
3.2	5.5	3.8	6.1	20	96	58	71	75	1,030	5.5	55	2,310	16	..	400
5.6	6.3	3.4	14.0	44	63	45	51	75	650	5.2	45	3,160	..	52	...
3.7	9.3	5.1	13.0	40	99	65	71	84	610	5.6	95	3,480	12	..	...
...	...	...	12.6	40	...	..	..	..	.....	5.5	...	.....	..	..	200
5.6	2.9	1.8	8.6	29	105	45	54	103	1,250	5.1	70	1,710	..	..	...
5.2	...	...	7.8	26	103	45	52	103	.....	5.2	120	1,870	10	..	...
4.6	4.7	3.0	8.9	29	140	60	87	71	1,480	...	10	1,960	..	..	...
4.2	4.8	2.6	10.0	32	·71	42	50	75	830	5.4	25	2,660	..	290	...
3.7	5.4	2.9	8.9	28	122	63	83	84	1,230	5.8	65	3,080	16	..	150
4.9	5.1	3.1	13.5	40	77	46	54	77	850	4.8	65	2,970	..	90	...
4.1	7.7	4.6	12.3	35	100	63	74	97	770	5.6	140	3,360	13	..	175
...	...	...	....	36	80†	50	..	88	.....	5.6	...	2,160	..	250	...
...	...	...	....	32	76†	60	..	100	.....	6.0	...	2,400	9	..	...
...	...	...	....	31	88†	62	..	110	.....	6.0	...	.....	..	..	...
Patients with Stabbed Heart
5.8	5.4	3.2	11.0	34	84-100	60-68	72	88	1,070	6.2	135	.....	..	360	...
4.8	6.6	3.8	10.7	32	92-104	68	77	88	930	6.2	190	.....	..	..	...
...	...	...	....	32	...	..	..	..	.....	6.2	...	.....	..	..	...
5.8	3.4	1.9	17.7	45	83-100	51.54	64	88	1,500	5.9	160	.....	..	230	...
4.7	4.2	2.3	15.4	39	98-110	60	73	84	1,390	5.6	255	.....	..	..	...
Patients with Miscellaneous Conditions
2.8	5.5	4.2	10.4	33	83	49	61	-107	880	6.4	—10	2,500	..	..	...
2.0	10.9	8.3	....	23	109	60	81	111	590	5.3	+90	3,700	32	..	...
5.2	4.3	2.7	14.9	40	159	90	117	115	2,160	6.4	20	.....	..	..	...
5.9	3.0	1.9	13.0	38	148	84	98	94	2,510	5.9	10	.....	..	..	...
5.1	3.5	2.2	10.6	39	134	84	95	136	2,180	5.9	10	.....	..	..	...
4.3	5.9	3.7	....	33	180	96	126	136	1,710	5.5	55	.....	..	..	...
9.4	1.4	1.2	14.9	46	92	62	66	88	3,770	7.3	— 5	.....	..	..	...
6.3	2.5	2.1	12.8	40	154	88	105	88	3,310	7.8	+25	.....	..	..	200
4.0	6.5	4.3	15.5	50	140	89	107	167	1,320	6.9	0	.....	..	..	...
4.2	8.6	5.7	13.5	44	145	86	114	178	1,060	6.8	20	.....	..	..	850
1.9	13.9	9.1	....	..	130	89	103	188	600	6.5	10	.....	..	..	...
8.5	4.0	2.1	13.8	45	94	60	68	160	1,360	4.6	—10	.....	..	..	...
...	...	...	12.1	40	84	52	62	148	.....	5.7	+ 5	.....	..	..	...
...	...	...	11.5	37	89	55	66	144	.....	5.1	30	.....	..	..	...
7.0	4.9	2.6	10.7	36	96	58	70	150	1,140	4.9	10	.....	..	..	...
14.3	2.7	1.5	16.2	51	76	54	59	180	1,750	...	—25	3,100	..	..	...
7.0	8.5	4.7	13.3	44	101	63	73	168	690	...	+ 5	3,660	13	..	125
6.4	9.9	5.5	12.2	41	125	80	93	160	750	...	30	3,940	20	..	...
4.0	5.3	3.8	12.8	41	107	60	69	79	1,040	5.5	30	.....	..	..	...
4.1	5.0	3.5	10.9	36	107	57	71	67	1,140	5.0	105	.....	..	..	...
6.3	4.5	2.2	14.4	42	77	48	54	125	960	6.4	10	2,700	..	..	100
3.7	6.6	3.2	12.6	37	81	50	60	115	730	7.0	65	3,100	11	..	...
...	...	...	....	36	84	54	61	115	.....	6.6	70	3,200	12	..	...
...	...	...	9.6	30	82	49	56	107	1,040	5.6	— 5	2,140	..	..	...
6.4	4.3	2.2	7.7	24	93	49	62	94	670	6.2	+ 2	2,720	15	..	175
3.7	7.6	4.0	....	..	...	..	..	..	.....	...	...	.....	..	..	...
5.6	2.7	2.1	12.4	41	103	59	72	97	2,130	6.9	5	1,900	..	..	...
4.3	3.6	2.7	10.0	32	111	59	79	94	1,750	7.2	30	2,410	10	..	75
10.4	3.9	2.0	13.8	40	109	65	72	150	1,480	6.7	—35	.....	..	..	...
5.3	8.8	4.5	11.6	35	109	59	72	140	650	7.1	25	.....	..	..	100

tended to increase, though at times it remained unchanged or decreased. When the cardiac output increased, it did not appear to parallel the rise in atrial pressure, for it persisted as the atrial pressure fell.

HEMORRHAGE

Studies were made on 13 patients with circulatory insufficiency following acute hemorrhage (see table). Twelve of these patients had lost blood following knife wounds and one had bled from a peptic ulcer. All received 50 Gm. of a 25 per cent solution of human albumin except 1, who received 25 Gm. of albumin. Five of the patients were given from 125 to 300 cc. of isotonic solution of sodium chloride intravenously in addition to the albumin. The cardiac output was determined for 6 patients before any therapy, and for 5 of these after the administration of albumin. The time which elapsed between therapy and determinations of cardiac output varied from twenty to sixty minutes. The initial cardiac index varied from 1.6 to 3.1, with an average of 2.3. Following administration of albumin the cardiac index varied from 3.0 to 4.8, with an average of 4.0. The arterial systolic pressure increased in each instance except in patient C. R. The increase in cardiac output was proportionally greater than the increase in the mean arterial pressure, so that the peripheral resistance fell. There was no consistent change in heart rate.

Hemodilution occurred in each instance as reflected by the hematocrit reading and the concentration of hemoglobin and volume of plasma when measured. The volume of plasma was measured in 10 of the patients and found to be below the normal expected level in 8. The average increase in volume of blood per square meter of body surface following the administration of albumin was 417.0 cc. The average increase in volume of blood per gram of albumin given was 15.0 cc. Hematocrit studies showed that the hemodilution took place rapidly during and immediately after the administration of the albumin and continued at a somewhat lower rate during the hour following the therapy. There seemed to be little difference in the effect of the albumin in patients who received no added fluid and in those receiving up to 300 cc. of isotonic solution of sodium chloride.

INJURIES OF THE CHEST

Seven patients with rents of the parietal pleura were studied (see table). Six of these patients had received knife wounds shortly before they came to the hospital. The seventh, A. E., had received multiple fractures of the ribs as the result of an automobile accident twelve hours prior to the time of study. All of the patients had clinical evidence of circulatory insufficiency. The systolic arterial pressure was

below 100 mm. of mercury in each instance except that of patient A. E. In A. E. and P. D. the percentage saturation of the arterial blood with oxygen was 67 and 88 respectively.

Studies of cardiac output were made on 6 patients prior to any therapy and on 5 of these after the administration of albumin. Fifty grams of albumin in a 25 per cent solution was given to all except 1, who was given 25 Gm. The time which elapsed between therapy and measurement of the cardiac output varied from five to thirty-eight minutes. The initial cardiac index in the patients studied before and after therapy varied from 2.6 to 4.4, with an average of 3.4. The average cardiac index after therapy was 4.3.

The arterial pressure increased in each patient after the administration of albumin except in patient A. E. The peripheral resistance tended to be decreased before therapy and did not change significantly following therapy. The right atrial pressure consistently increased, and the heart rate of each patient increased except that of A. E., which remained unchanged.

The volume of plasma was measured in 6 of the patients and found to be below the expected normal value in 3. Hemodilution occurred in each patient as evidenced by the fall in hematocrit reading, in concentration of hemoglobin and in volume of plasma when measured. The average increase in volume of blood per gram of albumin was 12.6 cc.

STAB WOUND OF THE HEART

Two patients with hemopericardium resulting from penetrating wounds were studied (see table). N. B. was stabbed with an ice pick and S. W. with a knife. Both patients showed clinical signs of circulatory insufficiency, distended veins of the neck, paradoxic pulse and only slight excursions of the heart borders when examined fluoroscopically. Both cases were complicated by acute alcoholism.

Studies of cardiac output were made before and after the administration of human albumin. N. B. had a cardiac index of 3.2 initially and 3.8 after the intravenous administration of 25 Gm. of albumin in 500 cc. of isotonic solution of sodium chloride. The right atrial pressure increased from 135 to 190 mm. of water, and the arterial pressure became less paradoxic.

S. W. had a cardiac index of 1.9, which increased to 2.3 after the administration of 200 cc. of 25 per cent solution of human albumin intravenously. The right atrial pressure increased from 160 to 255 mm. of water, and his arterial pressure became less paradoxic. There was no significant change in heart rate, and the peripheral resistance was slightly lower in each instance following therapy. Hemodilution occurred in each instance as evidenced by the decrease in the hematocrit reading and in the concentration of hemoglobin.

In this clinic it is believed that the use of intravenous solutions results in improvement of the circulation in patients with pericardial tamponade from stab wound of the heart, even though the atrial pressure is elevated before therapy is started.[5]   A further rise in atrial and venous pressure by increasing the volume of blood allows the heart to fill better either by forcing blood out of the pericardial sac through the pericardial rent or by slight stretching of the pericardium.   Albumin appears to be the ideal material to use for this purpose in the emergency clinic.

A heterogenous group of patients with clinical signs of circulatory insufficiency were studied before and after the intravenous administration of human albumin.   We formed the clinical impression that all had hemoconcentration even though the hematocrit readings were below normal in some instances.   In the patients with burns and the reaction to oxophenarsine hydrochloride, the hemoconcentration resulted from extravasation of plasma; in the remainder, from dehydration.   The group consisted of 1 patient with loss of fluid from a stoma of the ileum, 3 patients with extensive burns of the body surface, 1 patient with generalized edema following the intravenous injection of oxophenarsine hydrochoride, 2 patients with pneumococcic pneumonia, 1 patient with generalized peritonitis which was thought to have been due to a ruptured appendix, 1 patient with hemorrhage after drainage of a periurethral abscess, 1 patient who had recently had the right kidney removed for renal tuberculosis and 1 patient who had been operated on for a gunshot wound in the abdomen.

One patient was given 25 Gm. of albumin in a 25 per cent solution; 5 were given 50 Gm., and 5 were given 75 Gm.   The average arteriovenous oxygen difference before therapy was 7.0, whereas after therapy the average was 4.4.   The average cardiac index was 2.6 and 4.5 respectively before and after therapy.   The mean arterial pressure increased after therapy except in 1 instance, in which it remained the same.   The heart rate decreased in 7 patients, increased in 3 and did not change in 1.

<div align="center">COMMENT</div>

The data on the normal subjects are of considerable interest.   They demonstrate again that a considerable increase in volume of blood over the normal level may be produced without an appreciable rise in arterial pressure.   The lack of correlation between the atrial pressure

5. (*a*) Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: Pericardial Tamponade from Stab Wound of the Heart and Pericardial Effusion or Empyema: A Study Utilizing the Method of Right Heart Catheterization, Am. Heart J., to be published. (*b*) Cooper, F. W., Jr.; Stead, E. A., Jr., and Warren, J. V.: The Beneficial Effect of Intravenous Infusions in Acute Pericardial Tamponade, Ann. Surg. **120**:822, 1944.

and the cardiac output noted in these data has been confirmed by observations concerning a large series of patients whose atrial pressure was raised by the rapid intravenous administration of isotonic solution of sodium chloride.[6] The significance of these observations will be fully discussed elsewhere.

The results of therapy in patients with hemorrhage were uniformly good. These patients demonstrate the simplest form of circulatory failure produced by injury. Blood is lost from the vascular bed; the atrial pressure and the cardiac output fall, and the arterial pressure finally reaches a low level. The cardiac output falls to a greater degree than does the arterial pressure, indicating persistence of arteriolar tone and well maintained peripheral resistance. When the volume of blood is restored, the cardiac output rises and the peripheral resistance decreases.

The patients with wounds of the pleura showed good hemodilution in response to the administration of albumin. Though these patients appeared clinically to have the same type of circulatory failure as did the patients with simple hemorrhage, analysis of the data on 13 patients with wounds of the chest shows certain significant differences.[7] The fall in cardiac output in these patients was not striking and was proportionately much less than the fall in arterial pressure. The atrial pressure did not usually fall below the normal level. This type of circulatory collapse has been shown to be the result of reflex loss of arteriolar tone.[8] In these patients loss of blood probably played a secondary role in producing the shock picture. A part of the sharp rise in arterial pressure observed after the administration of the albumin may well have occurred spontaneously.

The results of therapy in the patients with burns, dehydration and infection were satisfactory. The clinical condition of the patients improved as the circulation became more adequate.

Measurements of the blood volume of 21 patients were made before and after therapy. Between 100 and 200 cc. of isotonic solution of sodium chloride was always given to the patients in whom the cardiac output was measured, because the lumen of the catheter was kept patent by

6. Unpublished data from this laboratory.

7. Merrill, A. J.; Warren, J. V.; Stead, E. A., Jr., and Brannon, E. S.: The Circulation in Penetrating Wounds of the Chest: A Study by the Method of Right Heart Catheterization, Am. Heart J., to be published.

8. (*a*) Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: The Effect of Venesection and the Pooling of Blood in the Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observations on Acute Circulatory Collapse in Three Instances, J. Clin. Investigation 24:337, 1945. (*b*) Barcroft, H.; Edholm, O. G.; McMichael, J., and Sharpey-Schafer, E. P.: Posthemorrhagic Fainting: Study by Cardiac Output and Forearm Flow, Lancet 1:489, 1944. Merrill, Warren, Stead and Brannon.[7]

a slow continuous drip. The average increase in plasma volume produced by 1 Gm. of albumin was 14.0 cc. Four of the 21 were patients with dehydration who were given a 25 per cent solution of albumin with a minimum of added fluid. In these 4 patients the average increase in volume of plasma produced by 1 Gm. of albumin was 13.0 cc. It appears that fluid is drawn into the blood stream in effective amounts even in the presence of moderate dehydration. In a preliminary report from this laboratory it was found that 16 cc. of fluid was retained for each gram of albumin.[9] Other workers have reported an average increase in volume of 17.4 cc. per gram of albumin.[10] The increase in volume of blood per gram of albumin will be influenced by the degree of loss of plasma, the state of hydration of the patient and the amount of fluid given parenterally or by mouth before, during or after the infusion of albumin. In a few hours the body can add or remove enough protein from the blood stream significantly to change the volume of plasma. If excess albumin is given, it may be removed by the body, a circumstance which would alter the apparent efficiency of the albumin.

The concentrated solution of albumin was given rapidly to most of the patients. To 11 patients 50 Gm. was administered in fifteen minutes or less. The speed with which a large amount of protein can be given without reaction is one of the most attractive features of albumin therapy.

Recently it has been emphasized that albumin is not as useful in the treatment of shock as is whole blood.[11] With this we are in agreement. Neither plasma nor albumin is a substitute for whole blood. Albumin is nevertheless an extremely useful substitute for plasma. From the standpoint of speed and convenience of administration, convenient packaging, small bulk, stability under varying temperatures and absence of bacterial contamination, concentrated albumin is ideal. In civilian practice, where whole blood and plasma are readily available, albumin may not be used extensively in the treatment of shock, but under the

9. Warren, J. V.; Stead, E. A., Jr.; Merrill, A. J., and Brannon, E. S.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: IX. The Treatment of Shock with Concentrated Human Serum Albumin; a Preliminary Report, J. Clin. Investigation **23**:506, 1944.

10. Heyl, J. T.; Gibson, J. G., II, and Janeway, C. A.: Studies on the Plasma Proteins: V. The Effect of Concentrated Solutions of Human and Bovine Serum Albumin on Blood Volume After Acute Blood Loss in Man, J. Clin. Investigation **22**:763, 1943.

11. Cournand, A.; Noble, R. P.; Breed, E. S.; Lauson, H. D.; Baldwin, E. D.; Pinchot, G. B., and Richards, D. W., Jr.: Chemical, Clinical, and Immunological Studies on the Products of Human Albumin Fractionation: VIII. *Clinical Use of Concentrated Human Serum Albumin in Shock, and Comparison with Whole Blood and with Rapid Saline Infusion*, J. Clin. Investigation **23**:491, 1944.

conditions of war concentrated albumin has many advantages. It is possible that the danger of hepatitis resulting from transfusion of blood and plasma can be avoided by using albumin.

SUMMARY AND CONCLUSIONS

1. Human albumin was given to 7 normal subjects and to 33 patients with circulatory failure. There were no unfavorable reactions.

2. In the normal subjects a rise in right atrial pressure and a fall in the hematocrit reading always occurred. The changes in cardiac output were variable. The arterial pressure and pulse rate usually remained unchanged.

3. In patients with hemorrhage, wounds of the chest, pericardial tamponade, burns, dehydration and infection, satisfactory hemodilution occurred when albumin was given in concentrated form (25 per cent solution).

4. The average increase in volume of blood for the entire group per gram of albumin administered was 14.0 cc. Dehydration was present in 4 of these patients, and the average increase per gram of albumin was 13.0 cc.

5. Eleven patients received 50 Gm. of albumin in fifteen minutes or less. The fact that these large quantities of protein can be given so rapidly makes concentrated albumin solution a valuable material to have on hand in the accident ward.

6. Human albumin is a useful substitute for plasma. It cannot replace the use of whole blood, but its small bulk, the ease and rapidity of its administration, its stability at room temperature and the absence of unfavorable reactions make it useful in many emergencies.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1945

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THE electrical examination of the nerve and muscle has long been an important part of the neurologist's work. Since the days of Erb the determination of the reaction of muscle to faradic and galvanic stimulation has been the common practice. This gave qualitative results of value to the clinician, but the importance of changes of polarity was overemphasized, and the "R.D." (reaction of degeneration) was at best a rough test of function. Since this, "chronaxie" has had its day and failed to satisfy the needs of a useful clinical test. It is now replaced by two methods: (a) the determination of strength-duration curves, i. e., the relation of voltage to duration in time of the stimulus,[1] and (b) the measurement of the accommodation constants of muscles during regeneration by progressively modulated currents.[2]

It now seems possible that the improved technics of electromyography may supplant these other electrical methods for clinical diagnosis. Records of the action potentials of human muscles have been used for clinical diagnosis since the pioneer work of Piper,[3] but his method of using a string galvanometer with leads to electrodes applied to the skin led only to a few clinical contributions. Tremors were well shown,[4] and those due to neurologic lesions were differentiated from hysterical tremors.[5] Recently leads from the skin over muscles have been used by Harvey and Kuffler[6] to record muscular action potentials on an electrocardiographic apparatus. By stimulating the appropriate nerve at a point higher on the limb, they recorded electrical potentials in normal and in partially paralyzed muscles, compared

1. Ritchie, A. E.: Electrical Diagnosis of Peripheral Nerve Injury, Brain 67:314, 1944.

2. Pollock, L. J., and others: Electrodiagnosis by Means of Progressive Currents of Long Duration, Arch. Neurol. & Psychiat. 51:147, (Feb.) 1944.

3. Piper, H.: Ueber den willkürlichen Muskeltetanus, Arch. f. d. ges. Physiol. 119:301, 1907.

4. Salomonson, J. K. A. W.: Tonus and Reflexes, Brain 43:369, 1921.

5. Cobb, S.: Electromyographic Studies of Muscles During Hysterical Contraction, Arch. Neurol. & Psychiat. 4:8 (July) 1920.

6. Harvey, A. M., and Kuffler, S. W.: Motor Nerve Function with Lesions of Peripheral Nerves: Quantitative Study, Arch. Neurol. & Psychiat. 52:317 (Oct.) 1944; Synchronization of Spontaneous Activity in Denervated Human Muscle, ibid. 52:495 (Dec.) 1944.

the records and were able to measure the curves and give some quantitative idea of the return of function in such neural lesions as peripheral neuritis.

Fundamental work was made possible by the introduction by Adrian and Bronk [7] of the concentric needle electrodes that could be thrust through the skin into the muscles, where they could pick up potentials from single motor units or single muscle fibers. For years this method was used in physiologic research, but only recently was it taken over by clinical neurologists for the study of injuries to peripheral nerves and muscular weakness and atrophy. In Denmark Buchthal and Clemmesen [8] made beautiful electromyograms of different muscular affections, especially those causing atrophy. In this country Brazier, Watkins and Schwab [9] have studied the electromyographic changes in poliomyelitis, neural injuries and polyneuritis. These authors are especially careful in their terminology and define important terms as follows:

Fibrillation: the involuntary contraction (or the electrical potential resulting from the contraction) of a single muscle fiber. This fibrillation is only found in denervated muscle. Electrically it is a potential change of such short duration (one to two milliseconds) that it cannot be recorded by an inkwriting oscillograph. One needs a cathode ray oscilloscope to record it. Its voltage is rarely above 50 microvolts.

Fasciculation: the involuntary contractions of those muscle fibers served by one motor unit (i. e., the twitches seen by the neurologist in such diseases as amyotrophic lateral sclerosis and usually loosely described by him as "fibrillations"). These fasciculations are motor unit potentials and are of longer duration than fibrillations (e. g., five to ten milliseconds) and are therefore easily recordable with an inkwriting oscillograph. They may be of quite high voltage (500 microvolts).

Action potential: those potentials produced by voluntary action (i. e., contraction) of the muscle (never spontaneously occurring dis-

7. Adrian, E. D., and Bronk, D. B.: *Discharge of Impulses in Motor Nerve Fibers: Frequency of Discharge in Reflex and Voluntary Contractions,* J. Physiol. **67**:119, 1929.

8. Buchthal, F., and Clemmesen, S.: On the Differentiation of Palpable Muscle Affections by Electromyography, Acta med. Scandinav. **105**:48, 1940; On the Differentiation of Muscle Atrophy by Electromyography, Acta psychiat. et neurol. **16**:143, 1941.

9. Watkins, A. L.: Electromyographic Studies in Poliomyelitis, Journal-Lancet **64**:233, 1944. Brazier, M. A. B.; Watkins, A. L., and Schwab, R. S.: Electromyographic Studies of Muscle Dysfunction in Infectious Polyneuritis and Poliomyelitis, New England J. Med. **230**:185, 1944. Watkins, A. L., and Brazier, M. A. B.: Studies on Muscle Innervation in Poliomyelitis and Nerve Injuries, Arch. Phys. Med. **26**:69, 1945; Observations on Muscle Spasm in Poliomyelitis, ibid. **26**:325, 1945.

charges in a muscle at rest). In this Brazier and her colleagues differ with Weddell, who is confusing in the field of regenerating nerve, where two phenomena may be present together: (1) spontaneous fasciculations in the muscle at rest, denoting regrowth of some nerve fibers to that muscle, and (2) action potentials produced by voluntary attempts at contraction of the muscle, denoting either some remaining intact fibers or some completely regenerated ones already capable of function.

Weddell, Feinstein and Pattle [10] have published a comprehensive paper on "Electrical Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions." They somewhat modified Adrian's coaxial needles, using hypodermic needles of gages 20 to 26 and from ½ inch (1.27 cm.) to 3 inches (7.62 cm.) long. With these as pairs of electrodes in the muscles (the core being the one and the hollow shaft the other of the pair) the currents were led off to an oscillograph, and the results were either seen or recorded by the oscilloscope or heard over a loud-speaker, the latter being the most useful for diagnostic purposes.

Their preliminary work on normal muscles in man indicates that a motor unit in voluntary (striated) muscle consists of a single discrete group of contiguous muscle fibers innervated by one neuron. The average size of the discharge potential of a motor unit in a limb muscle is larger than in facial and laryngeal muscles; it is usually monophasic or diphasic, with a duration of five to ten milliseconds. The fibrillation potentials [11] of denervated muscle are shorter, sharper diphasic spikes of a duration of only one or two milliseconds and an amplitude of not more than 100 microvolts, whereas motor unit action potentials which occur in normal muscle or voluntary contraction may have an amplitude ten or twenty times greater. These small spikes recorded from denervated muscles are the fibrillation potentials studied by Denny-. Brown and Pennybacker [12] in 1938. They believe that the fibrillation seen in muscles undergoing atrophy is due to rhythmic twitches of a single muscle fiber. These become sensitized by· neural atrophy, and small amounts of acetylcholine circulating in the normal circulation set them off. The potentials obtained from fasciculating muscles in men suffering from amyotrophic lateral sclerosis and from traumatic section of nerves are unlike those shown by experimental animals with denervated muscle. When a denervated muscle has undergone

10. Weddell, G.; Feinstein, B., and Pattle, R. E.: Electrical Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions, Brain **67:** 178, 1944.

11. Weddell's use of the term "action potentials" for the fibrillations of denervated muscle seems to me misleading—for a completely denervated muscle is incapable of "action" on any voluntary basis.

12. Denny-Brown, D., and Pennybacker, J.: Fibrillation and Fasciculation in Involuntary Muscle, Brain **61:**311, 1938.

fibrosis, no fibrillation potentials can be obtained. The number and frequency of these potentials are increased by heat and neostigmine. Muscles that have long been splinted show little fibrillation, while those that have had adequate physical therapy are likely to fibrillate actively.

Totally denervated muscles can be distinguished from those with partial lesions of the nerve, the former showing only fibrillation spikes in the electromyograph and the latter mixtures of these with motor unit potentials. The relative amount of each gives an indication of the extent of nerve injury.

Particularly interesting are the observations on such common clinical conditions as "Saturday night paralysis," "crutch palsy" and "Bell's palsy." These are generally considered to be due to pressure on the nerve, but Denny-Brown and Brenner [13] have shown that it is not the pressure on the axons that stops conduction, but the pressure on vessels, causing ischemia of the nerve. Weddell and his colleagues combine such clinical conditions under the functional diagnosis "reversible ischemic block." With the electromyograph, "insertion" motor unit potentials can always be obtained in these cases on insertion of the needle, and·it is usual to find few repetitive motor unit potentials which may or may not be under voluntary control. On the other hand, fibrillation potentials are few in number or absent. Such a picture gives a good prognosis for rapid recovery.

The time of change from motor unit potentials to fibrillation spikes in a denervated human muscle is variable. Roughly speaking all motor unit activity seems to be lost fifteen to twenty days after the neuronal lesion, while fibrillation spikes may begin to appear as early as the tenth day. The time needed for reinnervation of course depends on the location of the lesion. If the lesion is central (inside the dura) and if it is complete, no regeneration will occur. If the lesion is peripheral and the neural injury a clean cut with good surgical repair, the time of reinnervation depends on the distance of the neural injury from the muscle, the rate of growth of the axons being probably 1 or 2 mm. a day. When reinnervation begins in a muscle, the number of fibrillation spikes decreases in the electromyograph, and a few motor unit potentials appear in response to an effort to contract the muscle, as well as spontaneous motor unit potentials at rest. This is some days or weeks before the first contraction of the muscle can be seen clinically. The spontaneous motor unit potentials are small and polyphasic and are most numerous in the early stages of regeneration, but they may be found as long as eighteen months after reinnervation has begun. Experiments with neostigmine suggest that this drug facilitates neuromuscular transmission in early stage of reinnervation.

13. Denny-Brown, D., and Brenner, C.: *Paralysis of Nerve Induced by Direct Pressure and by Tourniquet*, Arch. Neurol. & Psychiat. **51**:1 (Jan.) 1944.

Weddell and his colleagues not only studied the many traumatic neural injuries of war, but also report on 37 cases of facial paralysis and show the usefulness of the electromyographic method in giving prognosis and indication for operation. They also discuss injury and disease of the spinal cord and show that electromyography can aid greatly in localizing the level of a lesion, in telling spinal from root lesions and in giving prognosis. In sciatica from prolapsed intervertebral disk the level of the lesion can sometimes be accurately determined by finding fibrillation spikes in the affected muscles. Watkins and Brazier [14] have used these technics successfully for locating the level of prolapsed vertebral disks in the cervical region.

In the course of this long and important paper Weddell and his colleagues take a fling at the vexed subject of "tonus." They recall that in 1931 Sherrington suggested that the word be dropped from the scientific vocabulary because of its vagueness and multiple meanings. Even when the term is applied to skeletal muscle it describes a complex mechanism under one heading and gives a false impression, unless it is clearly understood that the clinician means nothing more than "the constant slight tension characteristic of healthy muscle, which offers a steadily maintained resistance to stretching." [15] This is a difficult thing to test clinically and diagnoses based on it are not very dependable even when the observations are made by experienced neurologists. Weddell's contribution to the subject is his observation that when a muscle is completely relaxed there are no potentials recorded by electromyography. He illustrates our understanding of muscle "tone" by enumerating the following factors that go to make for muscular resistance to passive stretch: (1) the amount of extravascular fluid in the muscle, (2) the degree of congestion of the muscle (intravascular fluid), (3) tightness of the fascia and mechanical elastic factors and (4) motor unit activity set off by stimuli from the nervous system.

The fourth factor is the one about which neurologists usually think without considering the other three, and Weddell's point is well taken that all must be considered. His discussion of the neurologic mechanism is confused by bringing in "the emotional, or conscious level" (which is not defined). As long as this supernatural ingredient is left in, the term "tonus" will stick. Weddell does not make it clear that the neurologic part of "tone" is simply reflex postural contraction from the various levels of the central nervous system. When this nervous mechanism is active, as it is in many muscles most of the time, potentials are recordable by the electromyograph.

14. Brazier, M. A. B.; Watkins, A. L., and Michelsen, J. J.: Electromyography in the Differential Diagnosis of Cervical Ruptured Disk, Arch. Neurol. & Psychiat; to be published.

15. Holmes, G.: Cerebellum of Man, Brain **62**:1, 1939.

No explanation of the electrical phenomena of muscle as seen in the electromyogram will be valid until more is known about the mechanism of muscular contractions. A great step in advance seems to have been made by Szent-Györgyi and his collaborators. Their work is summed up in a monograph entitled "Studies on Muscle."[16] Their studies on myosin threads and insect muscles have led them to picture the model of striated muscle as made up of long actin threads with myosin micelles attached to them and winding about them in a spiral fashion. The first change, when contraction occurs, is a change in ionic distribution which discloses itself in an electrical potential and contraction in volume. The contraction of actomyosin is fast and extensive because the fiber is an asymmetric system of which one half (the myosin) shrinks rapidly and causes the fiber to curl and contract in spirals, shortening and thickening the whole muscle mass.

THE MOTOR AREAS OF THE CEREBRAL CORTEX

The localization of function in the cortex of the brain has long been a field of productive investigation by physiologists and clinical neurologists. The admirable monograph on "The Precentral Mortor Cortex" from the University of Illinois, edited by Paul Bucy, presents a mass of important data but shows how little is really known about the functions of the brain.[17] Here are 605 pages devoted to a study of the motor area, the part of the cortex longest known and most accurately studied, and yet many important points are still unsettled about the cortical fields and their projections on lower neuronal levels. Chapter 2, by von Bonin, describes the cellular architecture of the precentral areas. Taken as a whole, this subsector of the cortex is the one that receives thalamocortical fibers from the ventrolateral nucleus of the thalamus, relayed from the dentate nucleus. In general he accepts the old Brodmann scheme for areas 4, 6 and 44 (fig. 1). Area 4 lies in and closely anterior to the fissure of Rolando (central sulcus) but is divided now by von Bonin into three subdivisions: 4 gamma, 4a and 4s. Area 4 gamma contains the giant motor cells of Betz. Area 4a is similar in structure to 4 gamma, but has no Betz cells. Area 4s has large motor cells in the fourth layer, not giant cells in the fifth layer as in area 4 gamma.

The pyramidal tract, i.e., that bundle of fibers that makes up the "pyramids" of the medulla oblongata, is not entirely understood. Only about one third of its constituent fibers come from the giant cells of Betz in the motor cortex. The origin of the other two thirds is still a

16. Szent-Györgyi, A.: Studies on Muscle, Acta physiol. Scandinav., 1945, supp. 25.

17. Bucy, P. C.: The Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol 4, nos. 1-4, p. 605.

matter for discussion. One thing can be emphatically stated, and that is that the old schematization of the motor mechanism into an "upper motor neuron" and a "lower motor neuron" is an oversimplification that is inaccurate and misleading, both physiologically and anatomically. Even in the pyramidal tract there are usually internuncial neurons between the corticospinal fibers and the ventral horn cells. In the extrapyramidal systems there are many of them. In fact, the extrapyramidal tracts are characteristically composed of series of neurons that only after several relays reach the ventral horn cells to discharge on the "final common path" to the muscle. Levin, who writes the chapter on "Efferent Fibers" in this monograph, describes three main motor projections from the precentral areas: first, the corticospinal tract, which rises exclusively from the motor area proper (area 4); second.
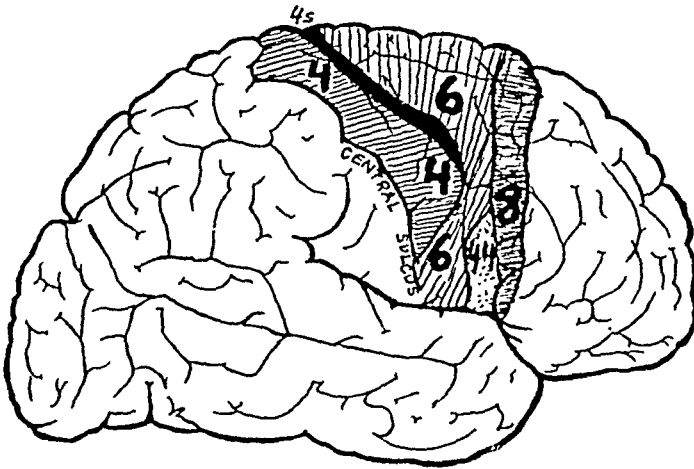
Fig. 1.—Brodmann's areas.

the corticonigral tract, from all parts of the precentral cortex (areas 6, 8, 4s and 4) to the substantia nigra in the brain stem, and third, the corticopontile tract, from all the motor areas to the nuclei of the pons. He states that small numbers of fibers pass from cortex to striatum, thalamus, zona incerta and red nucleus.

Kennard, in chapter 9, reproduces a diagram that shows direct fibers from areas 8 and 4s to the caudate nucleus, from areas 6 and 4 to the putamen and from 6 to the pallidum. Hines, in chapter 18, says that the origin of the tract from the frontal cortex to the pallidum is unknown, and that all areas of the motor cortex are related to each one of the main motor masses of the brain stem, except the corpus striatum. The function of the part of the pyramidal tract that arises in area 4 (according to Tower, who writes the chapter on "The Pyramidal Tract") is "somatotopically organized control of discrete movements," the extrapyramidal activity is on "a larger scale of distribution." What all this

signifies from the clinical standpoint is well expressed in a paragraph by Tower:

> As has been pointed out before, the lesions in man which produce the usual hemiplegia, or spastic paralysis, whether they lie in the cerebral cortex, internal capsule, or cord, are inevitably mixed pyramidal and extrapyramidal lesions, destroying fiber systems in both categories. And the symptomatology might be expected to be correspondingly compounded. The pyramidal elements in the total are easily recognized: loss of discrete control of the skeletal musculature, muscular atrophy, impaired or abolished superficial reflexes, and the sign of Babinski. But the muscular contractures, tonic neck reflexes, and the phenomena of spasticity are additional disorders, the consequences of extrapyramidal destruction.

From the normal physiologic viewpoint, Tower states that the pyramidal tract acts in two phases: There is a steady "tonic" innervation through all the waking hours which is a continual contribution to the central excitatory state of the spinal motor mechanisms, keeping them in readiness for the second of "phasic" activity which is episodic and appears as a specific contribution to individual motor acts.

In spite of differences in opinion concerning tracts and connections, the general consensus seems to be that area 4 has to do with discrete, learned movements ("pyramidal function"), and that areas 8 and 4s are "suppressor" in function. Area 6 is the main source of "extra-pyramidal" fibers; it lies between 8 and 4s and is bounded below by area 44. Stimulation of area 6 gives rise to sustained contraction and complex progressive and rhythmic movements; the threshhold of area 6 is higher than that of area 4. All the areas, including 4, have extra-pyramidal connections and functions. Area 44 subserves the delicate motor function of speech; lesions here may cause either dysarthria or apraxia, motor aphasia being synonymous with apraxia of the muscles of speech.

McCulloch's discussion in chapter 8 of the cortical connections as found by "physiological neuronography" is a fine piece of work that complements the anatomic studies and brings out connections not yet discovered by anatomic means. The author used the method of Dusser de Barenne, in which strychninization of the neural cells to be explored caused impulses to be set up which fired off electrical disturbances in the structure where the axon terminated. By picking up these characteristic potentials through an oscillograph the physiologic connections of one area with another were determined. O'Leary discusses in another chapter the relations between the form of the electroencephalogram and the anatomy of the cerebral structure. This is a good beginning in a difficult field.

More from the clinical standpoint Erickson discusses electrical stimulation of the cortex in man at operation, giving maps of the human

cortex with stimulable points. He mentions that the first stimulation was done by Robert Bartholow of Cincinnati in 1874. Bucy has two important chapters, one on extirpation in man and the other on the relation of the motor cortex to abnormal involuntary movements. Both are careful presentations of the data. In the latter the conclusions as to the sources of athetoid movements and of tremor are of necessity somewhat speculative. His theory of parkinsonian tremor is that such a tremor may develop because of interruption of a circular controlling mechanism which passes from the precentral motor cortex to the substantia nigra, globus pallidus, thalamus and thence back to the cortex. He mentions my theory [18] as an alternative. There seems to me to be no antagonism between our theories. I described the various extrapyramidal pathways between cortex and cord and postulated that partial interruption of internuncial neurons caused a disturbance in the normal asynchronous extrapyramidal impulses, leaving the field clear for a synchronous rhythmic discharge which caused tremor. Bucy's scheme of an interruption of a "circular controlling mechanism" might act in the same way.

Marion Hines writes the last chapter of the volume, giving a thoughtful and carefully worded exposition of the "Significance of the Precentral Motor Cortex." She differs from some of the other investigators by saying that there are no fibers from areas 6 to area 4 and no projection fibers from any part of the "precentral subsector" to the striatum. In her discussion of stimulation experiments she expresses the view that single muscles can be stimulated from points in area 4, but holds that this does not demonstrate the ability of that region to produce movement per se, that it only demonstrates what a certain electrical current can do. She believes that the sine wave current gives the best results. Muscles may be represented in more than one point and at one point more than one muscle may be made to contract, but one muscle is predominantly represented. Moving forward from area 4 (using the sine wave current at threshhold), the isolated focal movements are lost and more synergic movements appear, i.e., the extrapyramidal type. Hines points out that many otherwise good investigations of motor function have lost much by not describing muscular movements in an orderly and objective fashion. According to her a skilled act is performed by: (a) the discrete movements of intact musculature, called the prime mover, (b) cooperating movements of more proximal muscles, (c) fixation and holding contractions at the girdle and (d) contractions of antagonistic muscles. These factors may be seen clinically in normal and pathologic movements and may be produced to some extent as isolated phenomena in stimulation experiments.

18. Benda, C. E., and Cobb, S.: On the Pathogenesis of Paralysis Agitans, Medicine 21:95, 1942.

It seems to me that the much argued question as to whether the "motor cortex innervated muscles or movements" has not yet been answered. The evidence strongly suggests, however, that the normal function of the motor cortex always has to do with movements, although artificial means of stimulation of area 4 can elicit contractions of single muscles or even parts of muscles.

Removal of a part of the motor areas causes more or less loss of function, i.e., paralysis or paresis. There is in addition a release of function causing the phenomena of "hypertonus, clonus, brisk and irradiating tendon reflexes and associated movements." Cutting the tracts in the pyramids of the medulla causes loss of only one of these, the associated movements. This is what one would expect, because the other "release phenomena" seem to be extrapyramidal functions and interruption of pathways would have to be at a high level, since "release" can only be explained if some of the large motor nuclei of the base of the brain are released from above.

Finally Hines sums up the function of the motor cortex in three remarkable paragraphs, as follows:

In conclusion, the significance of the precentral motor cortex lies in its ability to confer upon the individual who possesses it within an intact nervous system, choice of initiation of contraction of single muscles or their functional units. This initiation of contraction is accompanied by that of cooperating muscles, by fixation of more proximally lying muscles, and by graded contraction or relaxation of antagonists. In skilled performance directed to accomplish a given end, the "fusillade" innervation of the cooperating extremity is as important as the innervation of the active or leading extremity. This cortical tissue makes possible stopping a movement at a given degree of contraction, and starting it again at a degree of contraction necessary to follow through to the desired end easily and without effort. Stereotyped patterned movements, integrated at lower levels, can be utilized as parts or wholes. Postural patterns can be assumed, modified and shifted such that an undetermined move can be made easily and instantly. To be "on his toes" is more than a trite expression.

Posture must not only be maintained in an easy, natural way to free the hand for manipulation, but must also anticipate by its adjustments that next movement. Exquisite as the movements of the fingers are, they do not work alone. And the variants in cooperation of movement, in fixation and in the increment and decrement of tone of muscles of the trunk, of those which attach the extremities to the girdles, and of those of the proximal part of the extremities are as important as movements of the digits in the attainment of skilled movements. No violin or piano was ever played with the fingers and hand alone.

The precentral motor cortex is not an isolated piece of nervous tissue sending out its impulses to lower motor centers. Its accomplishments are dependent upon the intactness of its thalamocortical relations. The instant obedience of muscles demanded in the performance of skilled movements is dependent upon intactness of other parts of the nervous system, in particular that of the basal ganglia and the cerebellum. The nice modulation of movement requires relation of this tissue to other cortical areas. The precentral motor cortex reaches out to constrain cooperation of its mirrored counterpart; it requests the contribution of the post-

central gyrus via fibers which run beneath its posterior boundary. It receives modifying impulses from all the somaesthetic sectors of the parietal lobe.

Taken as a whole this monograph, written by fifteen leaders in the field in eighteen chapters, is a great reference book for source material, but it leaves the reader with a certain confusion regarding disputed facts of observation and moot points of theory. The subject is complex. and difficult even though it concerns the simplest and best known part of the cortex. It is therefore with thankfulness that one turns to the short paper by Welch and Kennard on the "Relation of Cerebral Cortex to Spasticity and Flaccidity," [19] where a theoretic explanation is given briefly with a clarifying diagram. The authors state:

Certain preliminary observations on spasticity and flaccidity following removal of various areas of the sensorimotor cortex in monkeys led to the present investigation. These were (i) although removal of area 6 caused spastic paresis and removal of area 4, flaccidity, simultaneous removal of both areas produced greater spasticity than did excision of area 6 alone; (ii) primary removal of the postcentral gyrus caused flaccidity with minimal paresis; (iii) removal of an entire hemisphere caused more marked spasticity and paresis than did removal of the motor and premotor areas alone. . . .

It has also been established that primary injury to area 6 results in reflex grasping and slight increase of resistance to passive flexion and extension. If area 4s, lying between areas 4 and 6, is destroyed, alone or in combination with area 4 or area 6, spasticity results. Furthermore, lesions to area 6 intensify ipsilateral spasticity and bilateral removal of areas 4 and 6 results in great paresis and spasticity in all extremities.

The experiments performed by Welch and Kennard showed that in monkeys and chimpanzees removal of area 6, including 4s, was followed by moderate spastic paresis; removal of area 4 (excluding 4s) was followed by paresis without spasticity. Combinations of 4, 4s and 6 caused more spasticity; lesions of 4 combined with postcentral ablation caused some spasticity. These data are summed up in their figure 3 (here reproduced as fig. 2). The pyramidal fibers (represented as block pyramids with axons projecting downward) act directly on the motor cells of the cord at or near the final common pathway to direct fine volitional movements. The extrapyramidal fibers (represented by black circles with axons) act on subcortical nuclei integrating postural and locomotor adjustments. When the predominantly pyramidal areas are removed, there is paresis with little or no increased resistance to passive manipulation; when the areas are largely extrapyramidal, there is spasticity. Combinations of lesions add to the spasticity because more extrapyramidal neurons are injured. In terms of the diagram, the more black pyramids injured, the more paresis; the more black circles injured,

19. Welch, W. K., and Kennard, M. A.: Relation of Cerebral Cortex to Spasticity and Flaccidity, J. Neurophysiol. **7**:255, 1944.

the more spasticity, because removal of the circles releases the extra-pyramidal motor nuclei.

Lassek,[20] who has written several papers on the pyramidal tract, believes that general suppression of cerebral activity causes the Babinski phenomenon and that local pyramidal inhibition could do the same. This would correspond to the theory that the Babinski sign is caused by loss of pyramids, as in Welch and Kennard's diagram, a satisfactory theory for the present.
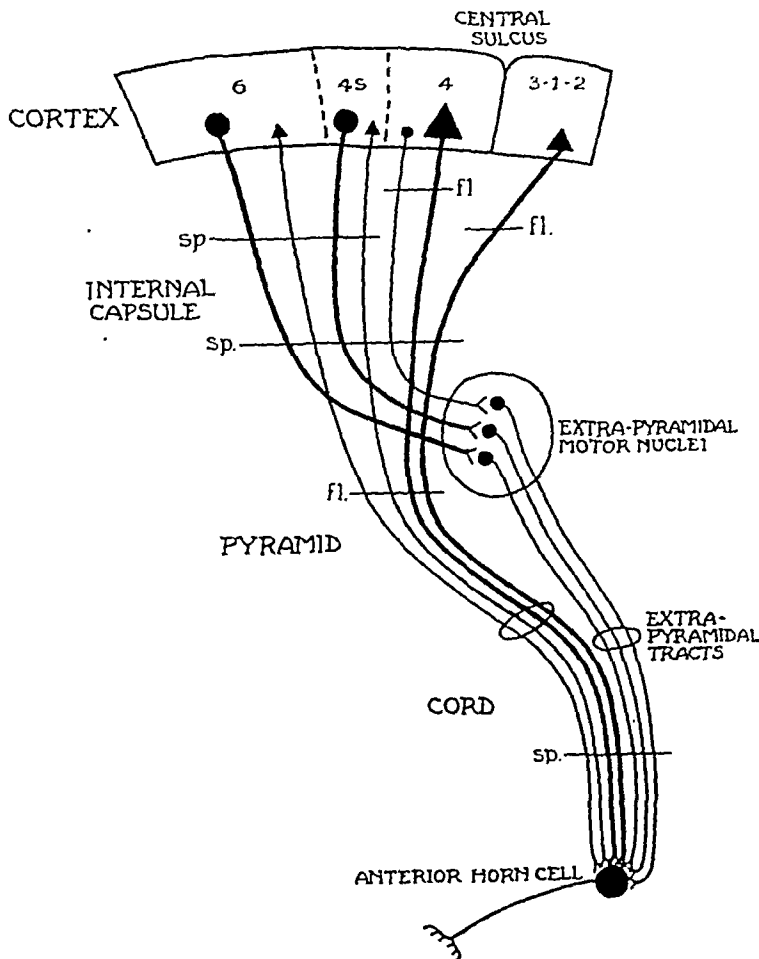
Fig. 2.—Diagram of pyramidal and extrapyramidal pathways. (*From the Journal of Neuropsychiatry, 7:255, 1944, by permission of Charles C Thomas, Publisher.*)

CONCUSSION OF THE BRAIN

In warfare since the Stone Age and in civil life since the advent of the automobile, cerebral concussion has been a great medical problem.

20. Lassek, A. M.: Human Pyramidal Tract: XI. Correlation of the Babinski Sign and the Pyramidal Syndrome. Arch. Neurol. & Psychiat. **53**:375 (May) 1945.

What is it that "knocks a man out" so quickly and completely, often with little or no subsequent disturbance? Three recent papers, two by Walker and his colleagues [21] and the other by Denny-Brown,[22] throw new light on the subject and decribe mechanisms which have physiologic meaning to replace the old vague theories of vascular paralysis, waves of fluid pressure, molecular shock and synaptic dysfunction.

The best clinical definition is that of Trotter [23]: "An essentially transient state due to head injury which is of instantaneous onset, manifests widespread symptoms of purely paralytic kind, does not as such comprise any evidence of structural cerebral injury, and is always followed by amnesia for the actual moment of the accident." The instantaneousness and transitory nature are here emphasized, which distinguish the condition from cerebral contusion, which may result from slow pressure, without loss of consciousness, although the pathologic lesions of contusion and laceration may sometimes accompany concussion. The subject under discussion here, however, is concussion that shows no gross or microscopic lesions of the brain at autopsy ·a few hours after the accident. This proviso as to time is made because Windle, Groat and Fox [24] have observed chromatolysis of nerve cells beginning fourteen hours after concussion and progressing to the sixth or eighth day. These changes are probably largely reversible, but some nerve cells may be destroyed.

Denny-Brown emphasizes that concussion occurs when the head is thrown suddenly and violently into motion or is suddenly stopped when in motion. He speaks of this as "acceleration concussion" and shows by his experience on animals that it occurs regularly when a pendulum at a velocity of 28 feet a second strikes a movable head. Calculations of the impacts that caused traumatic amnesia in man show that the velocity was 24 feet per second or greater, so that the critical speed of acceleration or deceleration is probably something of this order of magnitude.

When this kind of concussion occurs, the experiments show that there is a sudden brief rise of intracranial pressure with condensation of the substance of the brain. It is this sudden physical condensation of nervous tissue which is important. Electroencephalograms show that there is a short explosion of potentials of high voltage followed by a

21. (*a*) Walker, A. E.: Syndrome of Cerebral Concussion, Clinics **4**:361. 1945. (*b*) Walker, A. E.; Kollros, J. J., and Case, T. J.: Physiological Basis of Concussion, Physiol. Rev. **25**:296, 1945.

22. Denny-Brown, D.: Cerebral Concussion, Physiol. Rev. **25**:296, 1945.

23. Trotter, W.: Certain Minor Injuries of the Brain, Lancet **1**:935, 1924.

24. Windle, W. F.; Groat, R. A., and Fox, C. A.: Experimental Structural Alterations in the Brain During and After Concussion, Surg., Gynec. & Obst. **79**:561, 1944.

prolonged period of decreased electrical activity and raised threshhold to all stimuli. In other words, there is a sudden intense period of widespread nervous excitation followed by lack of response. The clinician might correlate these with the "seeing stars" and the following paralysis and amnesia. That the stimulus and following inactivity are widespread in the central nervous system is shown by the clinical observation of paralysis affecting all levels from the higher "conscious" mechanisms to the vegetative levels expressed in dilated pupils, apnea and vasoconstriction. The electroencephalograph shows that the cerebrum is widely affected, and Denny-Brown's observation that concussion can occur in decerebrate animals proves that lower centers are also involved.

Walker and his co-workers [21b] do not believe that acceleration is an essential factor, and emphasize that concussion is a direct mechanical and widespread effect on nerve cells causing excitation and discharge. Their ingenious and beautifully executed electroencephalographic experiments support this contention. To me the argument as to whether the phenomena of concussion are "excitatory" or "paralytic," or due to "acceleration" or "compression" seems largely semantic. The point is that commotio cerebri has been taken from the realm of speculation and given by all these investigators a specific physical and physiologic basis. When more is known about the nature of the nerve impulse and electrons, the process of concussion may be expressed in terms of polarized cell membranes and positive and negative charges, but that time is still far ahead.

PSYCHOPATHIC PERSONALITY AND EPILEPSY

"Experience in the war has demonstrated very clearly that incorporation in a disciplined force with rigid standards will often exhibit inadequate and aggressive individuals as sociopathic failures or delinquents." This quotation from Curran and Mallinson's review [25] of the "Psychopathic Personality" brings up a problem which has been of great importance in the armed forces. Although much less is written about them, some statistics show [26] that "psychopaths" were more common than "neurotics" in the military hospitals and training centers.

The misuse of the term "psychopathic personality" by persons not trained in psychiatry is a great difficulty, because to most people and

25. Curran, D., and Mallinson, P.: Recent Progress in Psychiatry: Psychopathic Personality, J. Ment. Sc. 90:266, 1944.

26. Hall, R. W.: Peculiar Personalities, War Med. 1:383 (May) 1941. Wittson, C. L.; Harris, H. I.; Hunt, W. A., and Solomon, P.: Neuropsychiatric Examination of Recruits at the United States Naval Training Station, Newport, R. I., War Med. 2:944 (Nov.) 1942.

to many physicians the term signifies anybody who is mentally abnormal, no matter what the diagnosis. Prue [27] says:

> The unsatisfactory state of the concept of psychopathic personality illustrates the futility of orienting psychiatric research about the traditional clinical entities as "diseases" of nineteenth century psychiatry. What is needed is a clear description of various problems of behavior expressed in simple unambiguous language. It would thus be possible to undertake a common sense attempt to specify the etiologic factors without preconceived bias. Having done this, one could approach the problems of prevention and treatment in a logical, systematic fashion.

Many psychiatrists, however, use the term "psychopathic" in a quite definite way. There are two main types, the inadequate and the aggressive. Both are fundamentally unreliable; "the truth is not in them." In spite of good intelligence they do not seem to be able to look ahead and realize the probable results of their acts. They live largely for the moment, and are plausible, talkative and often very beguiling at the beginning of an acquaintance, but they are disappointing and in the end "let their friends down" by lying, stealing and fugitive behavior. They are the "rolling stones" of literature, the "moral imbeciles" of an earlier psychiatric nomenclature. Many take to alcohol, many have unorthodox sex habits and most get into the hands of the police. None of them hold a job long. They are tramps, bums, hoboes, confidence men, men about town and occasionally, like Wilson Mizner,[28] earn much money and spend it lavishly.

It is no wonder that people of this sort when put into a permanent, disciplined situation like the army find themselves continually at odds with authority. Like Kipling's "Tramp Royal" they must restlessly move on:

> Speakin' in general, I 'ave tried 'em all—
> The 'appy roads that take you o'er the world.
> Speakin' in general I 'ave found them good .
> For such as cannot use one bed too long,
> But must get 'ence the same as I'ave done,
> · An' go observin' matters till they die.

Responsibility, security and routine are to them anathema.

The older theory was that they were "constitutional psychopathic inferiors," born that way with bad genes. More recently some psychiatrists have looked on them as "neurotic characters," and psychoanalysis has been futilely tried to reorganize their personalities. Now evidence is coming to the fore that many of them are victims of cerebral injury, including trauma, inflammation or agenesis, and show abnormal electro-

27. Prue, P. W.: Concept of Psychopathic Personality, in Hunt, J. McV.: Personality and the Behavior Disorders, New York, The Ronald Press Co., 1944, p. 922.

28. Johnston, A.: Legend of a Sport, The New Yorker, Oct. 10, 1942, p. 21.

encephalograms.[29] It has been long known that the postencephalitic "problem child" frequently had an abnormal electroencephalogram and that the line between such children and epileptic persons was difficult if not impossible to draw. It now seems possible that many patients with the diagnosis of psychopathic personality are to be looked on as similar to some adults with epilepsy, whose sudden fugues might be considered exaggerations of the unpredictable behavior of the psychopath. In a few cases phenobarbital and diphenylhydantoin sodium have been of use in checking the psychopathic behavior. Doubtless many of these patients inherit inferior brains and are hopeless from the standpoint of therapy, and some may have defects in character of a psychogenic (environmental) origin. Recent opinion stresses the importance of etiologic diagnosis and management by institutionalization, social adjustment and drugs.

Lennox [30] has just published two papers dealing with the successful use of 3, 5, 5-trimethyloxazoladine-2, 4-dione, which is manufactured by the Abbott Laboratories under the trade name of Tridione. He says the drug is effective in controlling or greatly diminishing attacks of petit mal, myoclonic epilepsy or akinetic seizures. It is of no benefit in cases in which the seizures are mainly of the grand mal convulsive type. From the electroencephalographic standpoint it seems to do most good to the patients who show abnormality of the dome and spike type. The only untoward effect so far noticed is photophobia.

29. Gottlieb, J. S.; Knott, J. R., and Ashby, M. C.: Electroencephalographic Evaluation of Primary Behavior Disorders in Children, Arch. Neurol. & Psychiat. **53**:138 (Feb.) 1945. Silverman, D.: Electroencephalogram of Criminals, ibid. **52**:38 (July) 1944. Knott, J. R., and Gottlieb, J. S.: Electroencephalographic Evaluation of Psychopathic Personality, ibid. **52**:515 (Dec.) 1944.

30. Lennox, W. G.: Epilepsy, Clinics **4**:504, 1945; Petit Mal, Myoclonic and Akinetic Epilepsies and Their Treatment with Tridione, J. A. M. A. **129**:1069 (Dec.) 1945.

Book Reviews

Pulmonary Tuberculosis in the Adult. By Dr. Max Pinner. Price, $7.50. Pp. 579. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Dr. Pinner modestly states in his preface that this book is not a textbook and that the primary aim "is not to impart knowledge but to create understanding." None the less there is little of importance about pulmonary tuberculosis which is left unsaid in this interesting treatise by a man who has thought long and carefully on the subject. One of the valuable features is the thorough lists of references, which follow each chapter. The author uses the device of inserting after each title a short paragraph in which the substance of the article is abstracted. There are numerous excellent illustrations and indexes.

A Primer of Electrocardiography. New Edition. By G. E. Burch, M.D., and T. Winsor, M.D. Price, $3.50. Pp. 215. Philadelphia: Lea & Febiger, 1945.

A primer is either an elementary schoolbook or a brief introduction to any subject. It should be short, clearly written and interesting.

This primer of electrocardiography meets these requirements. It has been constructed mainly for students and as a supplement to the more elaborate texts on electrocardiography, which are now so numerous that every medical school library has several on hand. Its charm lies in its simplicity: The language is clear and not too technical or wordy; the illustrations are diagrammatic and easily interpreted, and the arguments are stated with the assurance and positiveness that students always like.

On the whole, this small book deserves considerable popularity. It is certain to make many friends.

Pediatric X-Ray Diagnosis. By John Caffey, M.D. Price, $12.50. Pp. 860, with 711 illustrations. Chicago: The Year Book Publishers, Inc., 1945.

This is an expensive book, printed in large type on smooth paper, so that it appears especially well dressed and stylish. What it has to say is clear and to the point, and the illustrations are admirable. There seem to be enough differences between the roentgenologic observations on infants and those on persons in later life to make such a volume useful. It describes especially well the congenital defects and the diseases of bone with which internists—and radiologists, too, for that matter—who work with adults have little acquaintance. It is an excellent work of reference and deserves high praise.

Pathology of Tropical Diseases: An Atlas. By J. E. Ash, M.D., and Sophie Spitz, M.D. Price, $8. Pp. 350, with 941 illustrations, 15 in color, on 257 plates. Philadelphia: W. B. Saunders Company, 1945.

Colonel Ash and his colleagues have done a noteworthy service to American medicine by producing this atlas of the pathology of tropical disease, since, as far as the reviewer knows, nothing approaching it in usefulness is readily available at a reasonable price. Short but authoritative discussions of the various diseases are followed by the plates, which include maps, photographs of patients, reproductions of roentgenograms and photographs of gross specimens and histologic sections. The reproductions are excellent, and the microscopic sections, many in color and of high magnification, really show what the reader wants to know. The diagrams of the life cycle of parasites are unexcelled. The book is well got up on fine paper, and there is an index. It is hard to restrict one's praise of this excellent compendium.

Clinical Parasitology. By Charles Franklin Craig, M.D., and Ernest Carroll Faust, Ph.D. Fourth edition. Price, $10. Pp. 871, with 305 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1945.

This book has long held such an outstanding position that little need be said beyond reemphasizing some of its excellent features. These include good paper and print, numerous illustrations (some in color), diagrams, maps, index both by names and by subjects and thorough bibliography. As the authors point out in their preface, the volume has been completely revised and several new chapters have been added. The material is conveniently arranged, and the text is written with the obvious authoritativeness of those who have worked long in the field.

The Fundamentals of Electrocardiographic Interpretation. Second edition. By J. B. Carter, M.D., Assistant Professor of Medicine, Illinois College of Medicine. Price, $6. Pp. xvii + 406, with 307 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Every year the ARCHIVES is likely to review at least two or three books dealing with electrocardiography. Each review is likely to be worded in much the same manner, emphasizing the author's wish to produce something of practical aid to the medical student or to the clinician. Each book on the subject that is reviewed is likely to follow much the same pattern: some sort of an historical account of the electrocardiograph, some account of the technical use of the instrument and a variety of neatly interpreted tracings.

THE ARCHIVES reviewed the first edition of this book (62:1096 [Dec.] 1938). It concluded by predicting that the book without doubt would be helpful to the student, although the book embodied nothing that gave it any advantage over hitherto published books on the subject. The new edition is longer than the first, contains more illustrations and is $1.50 more expensive to purchase. What was said of the first edition holds true for the second.

Essentials of Clinical Allergy. By Samuel J. Taub, M.D. Price, $3. Pp. 198. Baltimore: Williams & Wilkins, 1945.

This monograph is written intelligently by a clinician who is familiar not only with allergy but also with medical students and practitioners. It discusses allergy from several viewpoints, laying especial emphasis on those kinds of allergy which appear most commonly in clinical work. Thus the author has a great deal to say about asthma and hay fever but comparatively little about gastrointestinal allergy or migraine or arthritis. He gives an excellent account of the detective work needed to track down the cause in any given case and sensible advice in regard to treatment.

On the whole, the volume promises well to fulfil the purpose for which it was prepared: to make the field of allergy easily accessible to beginners or to physicians who cannot possibly read their way through the maze of literature on allergy. It deserves success.

Pulmonary Tuberculosis: A Handbook for Students and Practitioners. By R. Y. Keers and B. G. Rigden, with a Foreword by F. H. Young. Price, $5. Pp. 273, with 124 illustrations. Baltimore: Williams & Wilkins Company, 1945.

This little book presents an admirable systematic discussion of pulmonary tuberculosis. As the authors say in their preface, they have tried to present "the position of pulmonary tuberculosis today, incorporating the advances in diagnosis and treatment which have occurred in the last two decades." The discussion of collapse therapy in its various phases seems especially sane and well tempered. There is a large number of excellent reproductions of roentgenograms. The style is clear and precise. There is an index.

Bronchial Asthma. By Leon Unger, M.D. Price, $9.00. Pp. 730 +, XVI. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

This volume of 730 pages on bronchial asthma by Dr. Unger is unique if for no other reason than that one man was able to fill so many pages on this subject. There is little doubt but that this large volume is the most complete thus far available on asthma. Certain important considerations, however, are either lightly passed over or erroneously presented. In discussing a disease process as severe as asthma, one should surely devote more than 8 pages to the disturbed physiologic factors, the understanding of which is so important if one is to treat the patient in a rational manner. The same criticism also applies to the cursory handling of the complication. The statement on page 323 that digitalis is of little value in the treatment of cardiac asthma is not substantiated by modern medical thought.

In general, the chapters on the allergic and the nonallergic treatment are well handled, although one is astonished that a man of such wide experience as the author would advocate cutting the ragweeds on empty city lots to decrease the incidence of asthma.

There are many good illustrations, particularly those dealing with pathology. However, some, such as figures 83 *A* and *B* and 86 fail to indicate what the author wishes to show. One might also draw attention to the lack of uniformity in reproducing roentgenograms; that is, figure *6 A* is viewed in the anteroposterior position, while figure 67 is viewed in the posteroanterior position.

Of real value is the chapter on the contents of various patent medicines used in the treatment of asthma.

Government in Public Health. By Harry S. Mustard, M.D. Price, $1.50. Pp. 219. New York: Commonwealth Fund, 1945.

This handy book, written in not too technical language, presents an admirable survey of what public health is all about. The discussion of the historical development of public health measures in the United States is particularly valuable, and the division into chapters on federal, state and local health services simplifies an obviously complicated subject.

This treatise, the prospective reader should know, is sponsored by the Committee on Medicine and the Changing Order of the New York Academy of Medicine. It is one of a series of studies which, it is hoped, will help to orient those who see the need of progress in the various domains of medicine. It is to be hoped that this excellent study on government in public health, which emphasizes what has been achieved, will point out by implication some of the things which still need badly to be done.

Classic Descriptions of Disease. By Ralph H. Major, M.D. Third Edition. Price, $6.50. Pp. 727, with 137 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1944.

We already have reviewed the two previous editions of this book favorably (**50**:960 [Dec.] 1932 and **65**:1299-1300 [June] 1940).

The third edition is built on the lines of the first but is a little bigger, more profusely illustrated, and more expensive. There are included a few more classic descriptions of disease than appeared in the other editions, and now each new one is indeed a rarity, for all the familiar ones were long since used up. The short sketch of each writer which accompanies his classic description is sharply drawn, attempting only to reveal salient features; thus it avoids tedium.

An interesting innovation is the introduction of a bibliography, which is placed ahead of the index. Here one can find references to the best biographies that have been written about any of the contributors whose work is mentioned; this is an important and worth while improvement.

Clearly, we approve of this book. We repeat: It makes a fine addition to any library.

Annual Review of Physiology. Edited by James Murray Luck. Price, $5. Pp. 774 and vii. Stanford University, Calif.: American Physiological Society and Annual Reviews, Inc., 1945.

Like the previous "Annual Reviews of Physiology," this volume for 1944 is very good. The subjects covered are reviewed well. Such a review affords an opportunity for those who cannot follow the work in the physiologic literature to learn the important contributions made in the field. It also makes possible an opportunity for those in physiologic work to observe the data collected from many sources collectively, thus permitting a better evaluation. The complete bibliographies appended to each chapter serve as excellent references. Such a review is of great value to every worker in both the clinical and the preclinical medical sciences. It is recommended highly to all medical students, interns and residents, as well as to practicing physicians, who tend to neglect the problem of applied physiology.

Essentials of Body Mechanics in Health and Disease. By Joel E. Goldthwait, M.D.; Lloyd T. Brown, M.D.; Loring T. Swaim, M.D.; John G. Kuhns, M.D., and William J. Kerr, M.D. Fourth edition. Price, $5. Pp. 316, with 128 illustrations. Philadelphia: J. B. Lippincott Company, 1945.

This book, well printed and profusely illustrated with photographs, charts and diagrams, is the collaborative effort of acknowledged leaders in the field of orthopedics and body mechanics. The impact of abnormal posture and body mechanics on the various viscera and the diseases or disorders which may result are fully dealt with. Therapy is discussed in detail. There is an extensive bibliography. This book should be highly useful to the general practitioner in orienting him in a difficult field.

Textbook of Neuropathology. By Arthur Weil, M.D., Associate Professor of Neuropathology, Northwestern University Medical School. Second edition. Price, $5.50. Pp. 370, with 289 illustrations. New York: Grune & Stratton, Inc., 1945.

The first edition of this book appeared in 1933. *The Journal of the American Medical Association* (**101**:1262 [Oct. 14] 1933) reviewed it favorably, saying that it was to be heartily recommended as an authoritative introduction to the subject.

The second edition is modeled on the first but carries forward the knowledge of the central nervous system a new ten years. It continues to discuss the pathology of the nervous system from a broad biologic standpoint, and by necessity is largely a text of histopathology. The first edition was printed by Lea & Febiger. The printers of the second edition use type that is somewhat different; the format, illustrations and tables are good. On the whole, the second edition deserves the same comment that was given to the first: It can be heartily recommended as an authoritative introduction to its subject.

Treatment in General Practice. By Harry Beckman, M.D. Fifth Edition. Price, $10. Pp. 1070. Philadelphia and London: W. B. Saunders Company, 1945.

This book has enjoyed the distinction of being the most popular one volume work on treatment since its first appearance in 1930. The author has periodically published new editions to keep the data abreast with the developments in therapy. This, the fifth edition, includes the newer advances in therapy. Clinical states which have become particularly important since the war, such as blast syndrome, chemical burns, airsickness, gas gangrene, human serum jaundice and shock, are discussed. Although some parts of the book have been rewritten, the method of presentation of the subject has remained unchanged. The reviewer recommends a consultation of this book whenever one wishes needed information on therapy. The book should continue to be one of the important books to be found in the library of any student or practicing physician.

Endocrinology of Woman. By E. C. Hamblen, M.D. Price, $8. Pp. 571, with 157 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

This book is well written. The presentation is concise; the organization of the material is logical, and the bibliography is adequate and up to date at the time of publication. For a textbook of endocrinology the absence of humbug is notable.

The author has presented his material in five parts. Part 1 is concerned with the history, embryology, anomalies, anatomy, chemistry, physiology and inter-relation of the various endocrine glands. This ambitious program is well executed in tabloid-like form with adequate annotations and references to support the text.

Part 2 is concerned with applied endocrine physiology: antenatal growth, sexual differentiation, childhood development, sexual maturation, sexual maturity and sexual regression, including chapters on menstruation, conception and gestation. The more recently acquired physiologic concepts are presented.

Part 3 is concerned with endocrine diagnostic methods. Normal values are given. The clinical significance of abnormalities is discussed.

Part 4 has to do with functional disorders of the endocrine glands. This part includes some of the weaker chapters in the book, probably because the author had to draw so largely outside his own clinical experience in discussing such disorders as those of the pancreas and the thyroid.

Part 5 is concerned with endocrinology applied to gynecologic disease. The author presents his therapeutic regimen for various endocrine disorders, including sterility. He makes no wild claims. He is refreshingly frank about the inadequacy of hormonal therapy for painful breasts and dysmenorrhea. On the other hand, there is an annoying tendency on the part of the author to present as fact a favorite hypothesis of his concerning the overactivity of the adrenal in the climacteric. Another failing is the absence of a coherent presentation of the problem of amenorrhea.

This book is recommended to students and practitioners.

Publicaciones del centro de investigaciones tisiológicas. Edited by Prof. Roque A. Izzo, Director. Volume 8. Buenos Aires, Argentina: Pabellon "Las Provincias," Hospital Tornu, 1944.

The eighth volume of research publications from the Hospital Tornu is a faithful continuation of their earlier volumes. This issue contains several valuable contributions on blood chemistry in tuberculosis, with a few academic studies on various normal and pathologic conditions. Some of the latter, together with an exhaustive review of the history of pneumothorax and a reinvestigation of the "leukocytic formulas" in tuberculosis, make the volume useful to those interested in these subjects.

The summaries in four languages of each article are commendable.

Endocrine Man: A Study in the Surgery of Sex. By L. R. Broster, D.M., F.R.C.S. Price, $3.50. Pp. 144. New York: Grune & Stratton, Inc.; London: William Heinemann, Ltd., 1944.

This work represents an attempt to define the role of the neuroendocrine system in a broad prospective by a British surgeon best known to this country for his work on the surgery of the adrenal glands in virilism.

The work is readable. There is no new material presented. However, the presentation of the author's concepts of instincts and of *symbiosis* is attractive and provocative.

The portion of the book most open to criticism contains the author's presentation of his favorite subject, the adrenogenital syndrome. He sponsors unilateral adrenalectomy for adrenal hyperplasia. He implies consistently excellent results. This hazardous procedure has few if any supporters in this country.

This book will be of more interest to biologists and those with special interests in endocrinology than to practitioners or medical students.

AMEBIASIS AMONG THE AMERICAN ARMED FORCES IN THE MIDDLE EAST

CAPTAIN EDWARD J. TALLANT

AND

CAPTAIN ALBERT L. MAISEL

MEDICAL CORPS, ARMY OF THE UNITED STATES

With Technical Assistance of First Lieutenant M. Ruth Rakestraw

ARMY NURSE CORPS, ARMY OF THE UNITED STATES

INTRODUCTION

THE RECENT American literature [1] has been placing increasing emphasis on the probability that American armed forces located in tropical and subtropical areas will return to the United States harboring many diseases acquired in these localities. A report of the Office of War Information [2] listed dysentery as the second greatest threat of disease among American overseas forces. Malaria headed the list.

This report covers the experience of a general hospital of the United States Army, located in the Middle East, with respect to amebic infection, during the period between Nov. 11, 1942, and Nov. 31, 1944. The present war is the first time that American troops have been stationed in this region in any considerable numbers. Amebiasis is hyperendemic in this area, principally because of the policy of using human feces as fertilizer. The host-parasite relationship, and thus the clinical picture, will not be similar in the native population and in our troops. As Faust [3] has pointed out, a host-parasite equilibrium develops in a population after long exposure, while fresh groups introduced into an endemic area will not have acquired a similar equilibrium and will therefore have a higher incidence of symptoms and a more manifest clinical picture.

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1. (a) Mackie, T. T.: Tropical Diseases: A Postwar Health Problem, New York State J. Med. 43:1509-1513 (Aug. 15) 1943. (b) Wright, W. H.: Present and Post-War Health Problems in Connection with Parasitic Diseases, Science 99:207-213 (March 17) 1944.

2. Health of the Armed Forces, J. A. M. A. 123:487 (Oct. 23) 1943.

3. Faust, E. C.: Some Modern Conceptions of Amebiasis, Science 99:45 (Jan. 21) 1944.

INCIDENCE

The incidence of amebiasis has been reported by authors from various parts of the world. Sapero and Johnson [4] found an incidence of 14.7 per cent among the United States Naval recruits from the Southern states and an incidence of 7.8 per cent among those from the Northern states. Wenrich [5] reported an incidence of 4.1 per cent among 1,060 college freshmen, while Rothman and Laskey [6] reported an incidence of 3.6 per cent in a survey of the staff of the Graduate Hospital of the University of Pennsylvania, Philadelphia, Strong [7] quoted Craig's report (1937) in which he found that of 57,561 persons examined in twenty-six different surveys in the United States an average of 10.2 per cent were found to harbor Endamoeba histolytica. Stitt [8] stated that, of nearly 7,000 British troops and civilians without any history of intestinal trouble examined in the Eastern Mediterranean area during World War I, 10.5 per cent were found infected with E. histolytica, while of 31,000 British troops returning to England from the Near East, the majority of whom had dysentery or other intestinal disturbances, 9.8 per cent were found infected. Bulmer and Priest, [9] reporting from a British General hospital in the Middle East, stated that, from March 1941 to September 1942, 4,178 patients with diarrheal diseases were admitted, 1 per cent of whom were infected with E. histolytica. Wright [1b] quoted a British report stating that about one eighth of the men hospitalized for dysentery cases in North Africa were infected with E. histolytica.

In an attempt to determine the incidence among the native population, in July 1943 we made microscopic examinations of suspensions in warm saline solution of the normally evacuated feces of 50 native workmen. All specimens were cultured in an attempt to determine the presence of pathogenic intestinal bacteria. The results of this examination are summarized in table 1.

4. Sapero, J. J., and Johnson, C. M.: Endameba Histolytica and Other Intestinal Parasites: Incidence in Variously Exposed Groups of the Navy, U. S. Nav. M. Bull. **37**:279-287 (April) 1939.

5. Wenrich, D. H.; Stabler, R. M., and Arnett, J. H.: Endamoeba Histolytica and Other Intestinal Protozoa in 1,060 College Freshmen, Am. J. Trop. Med. **15**:331-345 (May) 1935.

6. Rothman, M. M., and Laskey, M.: Survey of Protozoan Infection of the Staff of a Large General Hospital, Am. J. M. Sc. **206**:369-371 (Sept.) 1943.

7. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942, vol. 1, p. 477.

8. Strong,[7] p. 476.

9. Bulmer, E., and Priest, W. M.: Bacillary Dysentery: Chemotherapy in Its Treatment, Lancet **2**:69-71 (July 17) 1943.

One or more parasitic organisms were found in 90 per cent of the workmen. E. histolytica was present in 22 per cent, while 46 per cent harbored more than one organism. Since, as Faust[10] stated, only 20 to 25 per cent of cases of infections with E. histolytica are diagnosed by examination of a single direct fecal film, it is felt that this figure of 22 per cent is conservatively low. In a further attempt to investigate this situation, 25 Sudanese food handlers, whose stools showed no E. histolytica on routine microscopic examination, were given 30 cc. of a saturated solution of magnesium sulfate, and the purged stools were examined. Twelve, or 50 per cent of these, were found to harbor E. histolytica. By means of the technic of examining suspensions of the purged stool in warm saline solution, 167 Italian prisoners of war were examined prior to their acceptance as mess personnel. In 36, or 21.6 per cent, E. histolytica was found.

In the 38th General Hospital 77 members of the mess personnel, all

TABLE 1.—*Organisms Found on the Examination of the Feces of Fifty Native Workmen*

Organism	Patients	Per Cent
Ascaris lumbricoides	26	52.0
Endamoeba histolytica	11	22.0
Ancylostoma duodenale	11	22.0
Trichomonas hominis	7	14.0
Strongyloides stercoralis	4	8.0
Trichostrongylus colubriformis	2	4.0
Giardia lamblia	2	4.0
Schistosoma mansoni	2	4.0
Blastocystis hominis	1	2.0
Shigella paradysentery group	5	10.0
More than one organism	23	46.0
None	5	10.0

of whom were American soldiers, had purged stools examined each month during the entire period covered by this report. Of these, 28, or 36.4 per cent, were found to harbor E. histolytica on one of the examinations. In none of these 28 men was the organism found until the organization had been in this locality for approximately one year. Twenty-two, or 70.5 per cent, were entirely free of symptoms. Since routine examinations of purged stools were not performed on the entire personnel of the orginzation, it is not known whether this increased incidence among the food handlers was followed by an increased incidence among the remainder of the personnel.

Examination was made of either a purged stool or sigmoidoscopic washings of all of the members of the 38th General Hospital who complained of abdominal symptoms. Of the entire organization, 12 of 60 officers. or 20 per cent, 29 of 138 nurses, or 21 per cent, and 103 of 618

10. Faust, E. C.: Some Modern Conceptions of Amebiasis, Science **99**:69 (Jan. 28) 1944.

enlisted personnel, or 16.2 per cent (or a total of 144 of 816 personnel, or 17.8 per cent), were found to be suffering from symptomatic infection with E. histolytica during the two year period. This does not include the 22 food handlers without symptoms.

During the period covered by this report, 1,596 patients with enteric infections were admitted to the hospital. Of these 464, or 27.9 per cent, were infected with E. histolytica. Since all patients admitted to the hospital with intestinal dysfunction were examined for E. histolytica by the previously described technic, it is felt that relatively accurate figures were obtained so far as the hospitalized patients were concerned. However, due to the transient status of a considerable portion of the soldier population, no statistically accurate figures could be compiled for the entire population. My colleagues and I feel that the previously quoted incidence among the hospital personnel is a more or less accurate picture of the entire population. Using only those organizations which were permanently stationed in this area, we found that the admission rate for both patients with symptomatic forms of the disease and carriers was higher the second year than the first year. It is felt that this was due to the fact that a longer period of exposure increases the rate of incidence until an equilibrium is eventually established. The highest admission rate occurred in April and May of the second year. This is in agreement with the observations of Simon in the Gulf States, as quoted by Strong.[11] No correlation was found to exist between the rate of admission and the monthly variations in mean relative humidity. This is not in agreement with Strong's [11] statement that the seasonal variation is associated with variations in humidity.

PATHOLOGY

Since an understanding of the pathology of amebiasis is essential for a clinical appreciation of the disease, the highlights of the pathologic changes which occur will be discussed. In this brief résumé, Faust's [3] description of the lesions as they occur in the kitten, an animal easily infected experimentally, has been generally followed. The trophozoites, which are ingested, are killed by the gastric juices, while the cyst forms pass into the small intestines. If the condition of the small intestines, particularly the hydrogen ion concentration, is favorable, excystation occurs. Invasion of tissue by the newly formed trophozoites may or may not occur, depending on the motility of the intestinal canal and the amount of food present. An excessive amount of food prevents the organisms from coming into contact with the mucous membrane of the intestinal canal. Invasion of tissue usually occurs at the first point of stasis in the intestinal canal, the ileocecal region, although the organisms may be swept to the sigmoid region before penetration occurs. They may, at

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11. Strong,[7] p. 495.

times, pass completely through the anus without attachment. The site of highest incidence of penetration is the ileocecal region and the ascending colon, with the rectosigmoid region next in incidence, while the middle segment of the colon is rarely involved. The amebas penetrate the mucous membrane by means of a proteolytic ferment. There is a constant reparative process occurring simultaneously with the destructive process. This destructive-reparative balance is influenced by many factors, among which the following are the most important: first, the virulence of the organisms; second, the type of food in the intestinal canal, Hegner and Eskridge [12] having shown that a diet high in carbohydrates favors multiplication of the amebas while a diet high in animal protein retards their multiplication; third, secondary bacterial invasion which lowers the resistance of the local tissue, and fourth, the degree of host resistance based on group immunity, groups newly arriving in an endemic area having a higher incidence of symptoms and a more manifest clinical picture than the permanently resident population.

The pathologic process, and thus the clinical picture, in any given case is the result of this destructive-reparative balance. At times the lesions may be confined to the mucous membrane with extrusion of the organisms and complete healing, or there may be only the formation of shallow, microscopic ulcerations. After invasion of the mucous membrane there is first a lateral spread before penetration into the submucosa occurs. If the first lodgment is at the side or base of the crypt, there may be considerable erosion before hemorrhage occurs; if it is at the tip of the crypt, there is early contact with the capillaries and early hemorrhage. After the penetration of the submucosa there may be lateral spread and the formation of a bottleneck lesion with a small opening into the intestinal lumen, the typical amebic lesion. There is no leukocytic response to this early lesion. Following this, there may be extensive ulceration with gangrene of the wall of the bowel or there may be penetration to and through the peritoneum. There may be penetration of the intestinal mucosa and spreading to other organs, principally the liver and brain. It must be emphasized that penetration of the amebas through the intestinal·mucosa and spreading to other organs may occur without any demonstrable intestinal lesion and without any history of intestinal dysfunction.

SIGNS AND SYMPTOMS

As shown in table 2, the patients in this series have been divided into the following types: those with acute amebiasis, 49.2 per cent, who had no history preceding that which was the cause of admission;

12. Hegner, R. W., and Eskridge, L.: Influence of Carbohydrates on Intestinal Protozoa in Vitro and in Vivo, Am. J. Hyg. **21**:121-134 (Jan.) 1935; Elimination of Amoeba from Rats with a High Protein Diet, J. Parasitol. **23**:105-106 (Feb.) 1937.

those with chronic amebiasis, 12.9 per cent, who had a history of symptoms preceding the attack which led to admission; carriers, 26.1 per cent, who had no symptoms at any time; those with concurrent bacillary and amebic infections, 11.4 per cent, and those admitted because of complications of the disease .which, in this series, consisted only of hepatic abscesses, 0.4 per cent.

Table 3 shows the clinical picture at the time of admission to the hospital. No symptoms were present in 26.5 per cent of the patients; 35.7 per cent had mild signs and symptoms, consisting of fatigability, mild abdominal pain and either loose stools with a frequency of less than 5 per twenty-four hour period or normal stools; 13.4 per cent were severely ill, with toxicity, dehydration, elevation of temperature, nausea, vomiting and pronounced diarrhea, and the remaining 24.4 per

TABLE 2.—*Types of Patients*

Type	Number	Per Cent
With acute amebiasis	228	49.2
With chronic amebiasis	60	12.9
Carriers	121	26.1
With mixed infections (amebic and bacillary)	53	11.4
With hepatic abscess	2	0.4
Total	464	100.0

TABLE 3.—*Severity of Signs and Symptoms at Time of Admission*

Signs and Symptoms	Number	Per Cent
Lacking	123	26.5
Mild	166	35.7
Moderate	113	24.4
Severe	62	13.4

cent fell between these extremes and were classified as moderately ill. Thus, 62.2 per cent of the patients had either mild signs and symptoms or none at the time of admission.

The number of stools per twenty-four hour period, at the time of admission, is listed in table 4. There was no diarrhea in 41.8 per cent of the patients; 33.8 per cent had less than 5 stools per twenty-four hour period; 18.1 per cent had between 6 and 15 stools; 5.2 per cent had between 16 and 25 stools, and 1.1 per cent had over 26 stools per twenty-four hour period. The highest frequency was 50 stools, which occurred in 1 case. The majority of the patients with acute and chronic amebiasis had less than 5 stools per twenty-four hour period, while the majority of the patients with mixed infections had moderate diarrhea. Only patients with acute amebiasis had severe diarrhea. Moderate or severe diarrhea was not a characteristic in this series, as 75.6 per cent of the patients either did not have diarrhea or had less than 5 stools per twenty-four hour period.

As demonstrated in table 5, most of those patients who were clinically classified as severely ill at the time of admission had diarrhea to some degree. Of these, 43.5 per cent had less than 5 stools per twenty-four hour period while only 6.5 per cent had severe diarrhea.

Abdominal pain, usually mild and cramplike in character, was, as shown in table 6, the most consistent feature in the series, being experienced by 76.7 per cent of the patients with acute amebiasis, 81.6

TABLE 4.—*Number of Stools, per Twenty-Four Hour Period, at the Time of Admission*

Number of Stools per Twenty-Four Hours	Total		With Acute Disease		With Chronic Disease		Carriers		With Mixed Infections		With Hepatic Abscess	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
1	194	41.8	47	20.5	14	23.4	121	100	10	18.9	2	100
2-5	157	33.8	104	45.7	35	58.2	0	0	18	34.0	0	0
6-15	84	18.1	58	25.5	7	11.7	0	0	19	35.8	0	0
16-25	24	5.2	14	6.1	4	6.7	0	0	6	11.3	0	0
Over 26	5	1.1	5	2.2	0	0.0	0	0	0	0.0	0	0
Total	464	100.0	228	100.0	60	100.0	121	100	53	100.0	2	100

TABLE 5.—*Number of Stools per Twenty-Four Hours of Severely Ill Patients*

Stools per Twenty-Four Hours	Number of Patients	Per Cent
1	6	9.7
2-5	21	33.8
6-15	19	30.7
16-25	12	19.3
Over 25	4	6.5

TABLE 6.—*Incidence of Abdominal Pain and Tenderness*

Type Patient	Abdominal Pain		Abdominal Tenderness	
	Number	Per Cent	Number	Per Cent
With acute amebiasis	175	76.7	122	53.0
With chronic amebiasis	49	81.6	25	41.6
Carriers	0	0.0	0	0.0
With mixed infections (amebic and bacillary)	41	77.3	34	64.1
With hepatic abscess	2	100.0	2	100.0
Total	267	57.5	183	39.4

per cent of the patients with chronic amebiasis, 77.3 per cent of the patients with mixed infections and both of the patients with amebic hepatitis. It was present in 57.5 per cent of all patients, and it was experienced by approximately two thirds of the patients admitted with symptoms. In the hepatic abscesses the pain was located in the right upper quadrant of the abdomen while in the others it was located in either or both of the lower abdominal quadrants.

Abdominal tenderness, as shown in table 6, was present in 53.0 per cent of the patients with acute amebiasis, 41.6 per cent of the patients with chronic amebiasis, 64.1 per cent of the patients with mixed infections and both of the patients with hepatic abscess, or 39.4 per cent of all the patients. Thus, abdominal tenderness was present in approximately one half of those patients admitted with symptoms. In the cases of hepatic abscess the tenderness was located in the right hypochondrium. In 25, or 13.1 per cent of the patients with abdominal tenderness, or 5.3 per cent of all patients, the tenderness was most pronounced in the right lower quadrant of the abdomen, producing a clinical picture suggestive of appendicitis.

As shown in table 7, an elevation in temperature to between 100 and 104 F. was not an outstanding characteristic, as it occurred in only 20.6 per cent of the patients with acute disease, 13.3 per cent of the patients with chronic disease and 33.9 per cent of the patients with

TABLE 7.—*Incidence of Systemic Reactions—Elevation of Temperature and Leukocytosis*

Type of Patient	Elevation of Temperature (100-104 F.)		Leukocytosis (10,500-15,000)	
	Number	Per Cent	Number	Per Cent
With acute amebiasis	47	20.6	33	14.4
With chronic amebiasis	8	13.3	6	10.0
Carriers	0	0.0	0	0.0
With mixed infections (amebic and bacillary)	18	33.9	13	25.5
With hepatic abscess	0	0.0	0	0.0
Total	73	15.7	52	11.2

mixed infections, or 15.7 per cent of all patients. A leukocyte count between 10,000 and 15,000 was made for only a small percentage of the patients, 14.4 per cent of the patients acutely ill, 10.0 per cent of the patients chronically ill and 25.5 per cent of the patients with mixed infections, or 11.2 per cent of all the patients whose cases were reported.

Table 8 compares the patient's statement with the actual appearance of the stool with respect to the presence or absence of mucus and blood. Every stool in this series was examined by two persons, one of us and one member of the laboratory personnel. Of the patients with acute disease, 66.1 per cent, and of the patients with chronic disease, 56.6 per cent, showed neither mucus nor blood, while 85.2 per cent of the patients with acute disease and 78.4 per cent of the patients with chronic disease stated that they saw neither mucus nor blood. It is felt, therefore, that both the patient's statement and the gross appearance of the stool are of only limited value and are not diagnostic.

As shown in table 9, sigmoidoscopic examination was performed on 43.5 per cent of the patients with acute disease, 65.0 per cent of the

patients with chronic disease and 26.4 per cent of the carriers. This percentage was not due to any selection of cases but to the fact that there were no electric bulbs procurable for the instrument for a period of time. The wall of the bowel appeared normal in 10.1 per cent of the patients acutely ill, 10.2 per cent of the patients chronically ill and 75 per cent of the carriers. This figure is not surprising if one recalls that the involvement may be only in the cecal region and ascending colon. The wall of the bowel was acutely involved in 29.3 per cent of the patients with acute disease and 20.5 per cent of the patients with chronic disease. It was moderately involved in 60.6 per cent of the

TABLE 8.—*Gross Appearance of the Stool*

Type of Patient	Mucus		Mucus and Blood		Normal	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
With Acute Amebiasis						
Patient's statement............	10	4.5	24	10.3	194	85.2
Actual appearance..............	36	15.8	41	18.1	151	66.1
With Chronic Amebiasis						
Patient's statement............	8	13.3	5	8.3	47	78.4
Actual appearance..............	16	26.7	10	16.7	34	56.6

TABLE 9.—*Sigmoidoscopic Examination*

Appearance of the Wall of the Bowel	Patients with Acute Amebiasis		Patients with Chronic Amebiasis		Carriers	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Normal.........................	10	10.1	4	10.2	24	75
Acutely involved.................	29	29.3	8	20.5	0	0
Moderately involved.............	60	60.6	13	33.3	0	0
Scarred........................	0	0.0	14	36.0	8	25
Total examined..............	99	43.5	39	65.0	32	26.1

acutely ill and 33.3 per cent of the chronically ill patients. Those walls of the bowel classified as acutely involved appeared definitely inflamed, edematous, friable and discretely ulcerated; those classified as moderately involved exhibited discrete pinpoint ulcerations with relatively normal mucosa intervening. Of the patients with chronic disease 36 per cent, and of the carriers 25 per cent, showed scarring and pitting, the residuals of previous activity of the amebas. All of the patients with mixed infections showed a generalized inflammation of the wall of the bowel, due, probably, to the concomitant bacillary infection. In all cases showing acute involvement the clinical picture was severe. However, 2.5 per cent of those patients who appeared acutely ill had a normal-appearing wall of the bowel. Thus, in 132 of the 170 cases examined, or 78.9 per cent, there were suggestive sigmoidoscopic observations.

Since it is felt that a certain proportion of the American armed forces returning to the United States from endemic areas overseas will be suffering from chronic amebiasis, the prominent symptoms of this group are listed in table 10. The objective observations have been previously enumerated. It will be seen that 78.3 per cent of the group gave a history of intermittent diarrhea with occasional periods of constipation. The diarrhea, in most cases, consisted of periods of loose stools of two to three days' duration accompanied by mild, generalized abdominal pains without any periods of severe watery diarrhea. Those patients who gave no history of diarrhea complained of intermittent pain in the lower part of the abdomen, fatigability and pain in the lower part of the back.

As mentioned by Faust,[10] because of the higher incidence of involvement of the cecal and appendicular regions in tropical and subtropical areas, in many cases amebiasis is confused with appendicitis, and the

TABLE 10.—*Signs and Symptoms of the Patients with Chronic Amebiasis*

Signs and Symptoms	Number		Per Cent
Intermittent diarrhea and constipation............... (Forty days to three years)		47	78.3
No diarrhea		13	21.6
Intermittent abdominal pain......................	11		18.2
Pain in the lower part of the back...............	1		1.7
Fatigability	1		1.7
Abdominal pain......................................		46	76.6
Anorexia		23	38.3
Malaise		21	35.0
Generalized aches and pains...........................		11	18.2
Headache		5	8.3

patients operated on. He quoted Ochsner's report that 10 per cent of those in whom appendectomy was done at the Charity Hospital, New Orleans, had amebic involvement and the report of the Santa Tomas Hospital, Panama, of a 33 per cent frequency in the patients coming to operation for appendicitis. During the period covered by the present report, 273 appendectomies were performed at this hospital. Nine patients, or 3.2 per cent, had amebic involvement. Six were operated on and E. histolytica was subsequently discovered. Two were given a diagnosis of acute appendicitis at the operating table and the other 4 a diagnosis of enterocolitis. The other 3 were first treated for amebiasis and later operated on because of persistent pain and tenderness in the right lower quadrant. One of these, by barium sulfate enema, has shown a deformity in the region of the cecum, which operation revealed to be because the omentum was densely adherent to the medial wall of the cecum, probably the result of erosion of an amebic ulceration with "walling off" by the omentum. Histologic examination revealed chronic fibrinous appendicitis in the other 2. In one of the

9 cases was E. histolytica observed on microscopic examination of the tissues. We feel that in all cases in which acute appendicitis cannot be definitely ruled out, even if E. histolytica is discovered, a laparotomy should be performed, as the patient may have both amebiasis and appendicitis or there may be erosion of an amebic ulceration in the cecal region.

DIAGNOSIS

As emphasized throughout the literature, the only method of diagnosis is to find the causative organism, E. histolytica, in the feces. As shown in this report, the history, the physical examination, the sigmoidoscopic examination and the gross appearance of the feces were found to be only suggestive. Any or all of these may be normal. One must suspect amebiasis in every one who has resided in an endemic area, particularly if there is a history of vague abdominal pain, fatigability and loose stools alternating with normal stools.

Lincicome,[13] by examination of every stool of infected rhesus monkeys, and Tsuchiya,[14] by daily examination of the stools of a human carrier, have shown that there is a cyclic passage of the cysts of both E. histolytica and E. coli. James[15] summarized the situation when he stated, "It is . . . truly remarkable to see the variations in the number of amebas. . . . On one day the amebas will occur in great numbers and are easily found. On another day they will be uncovered only by a prolonged search in permanent preparations, and the fresh specimen will often be entirely negative." Svensson and Linders[16] recommended the rotuine examination of 10 successive specimens, while Dobell[17] recommended the examination of 6 successive specimens before pronouncing a given person free of the disease. Faust[10] stated that there is a 25 per cent chance of finding the organism in one normally evacuated stool of a person who is known to harbor it.

We feel that the examination of rectal washings obtained by means of a sigmoidoscope, while yielding a high percentage of positive results, cannot solely be relied on, as the infection may be limited to the cecal

13. Lincicome, D. R.: Fluctuation in the Numbers of Cysts of Endamoeba Histolytica and Endamoeba Coli in the Stool of Rhesus Monkeys, Am. J. Hyg. **36**:321-337 (Nov.) 1942.

14. Tsuchiya, H.: Observations on "Encystment Cycle" of Endamoeba Histolytica in a Carrier, Proc. Soc. Exper. Biol. & Med. **29**:930-932 (May) 1931.

15. James, W. M.: Diagnosis of Intestinal Amebiasis, J. A. M. A. **89**:1469-1472 (Oct. 29) 1927.

16. Svensson, R., and Linders, F. J.: The Chances of Detecting Infections with Intestinal Protozoa: A Parasitological Study and Statistical Survey, Acta med. Scandinav. **81**:267-324, 1934.

17. Dobell, C.: Amoebic Dysentery and the Protozoological Investigation of Cases and Carriers, Medical Research Committee, report no. 4, London, His Majesty's Stationery Office, 1917, p. 1.

region and the ascending colon, in which case the sigmoidoscopic findings may be normal. Likewise, cultural methods are reliable only in a positive sense, as excystation may not occur, while the complement fixation test is still of questionable value.

The diagnostic routine used in this series has consisted in the immediate microscopic examination of a suspension in warm saline solution of both the liquid stool and the sigmoidoscopic washings. Lugol's iodine stain has been utilized in the differentiation of the amebic cysts. If the patient did not have a liquid stool, and there were no contraindications, he was given 30 cc. of a saturated solution of magnesium sulfate in the morning, and the second liquid evacuation was examined. Three purged stools which were free of the organism, on three successive mornings, were required before the patient was pronounced either not infected or cured. By means of this technic, 71.6 per cent of the diagnoses of amebiasis were made by finding the trophozoites, 20.4 per cent by finding the precystic form and 8.0 per cent by finding the cystic forms of E. histolytica.

TREATMENT

Although there is some controversy as to whether or not the carriers, or so-called cyst passers, should be treated, all the patients in this series in whom E. histolytica was found were treated irrespective of the presence or absence of symptoms. This includes all the food handlers who were found to harbor E. histolytica as well as the hospitalized patients who were found to harbor the organism on routine examination. We are of the opinion that all are actual or potential sources of infection with the disease. The host-parasite equilibrium may be disturbed by many factors, among which are superimposed general or enteric infections and nutritional changes. There is also the likelihood that the disease may spread to other organs without any evidence of intestinal dysfunction for, as Craig[18] and Johnson[19] have pointed out, invasion of the tissue occurs in all cases, irrespective of the symptoms.

Depending on the availability of the amebicidal drugs, patients with acute and chronic amebiasis and patients with mixed infections were treated by one or the other of three plans of therapy. The patients with mixed infections received either sulfaguanidine, 3.5 Gm. every four hours for a total of 120 Gm., or sulfadiazine, 1 Gm. every four hours for a total of 30 Gm., concurrently with the amebicidal drugs with no ill effects.

18. Craig, C. F.: The Pathology of Amebiasis in Carriers, Am. J. Trop. Med. **12**:285-299 (July) 1932.

19. Johnson, C. M.: Observations on the Natural Infections of Endamoeba Histolytica in Ateles and Rhesus Monkeys, Am. J. Trop. Med. **21**:49-61 (Jan.) 1941.

The preferred plan of therapy consisted in the single daily intramuscular administration of 0.064 Gm. of emetine hydrochloride for six days with the concurrent oral administration of 0.25 Gm. of carbarsone three times a day for seven days. Following this, 0.6 Gm. of Diodoquin (5,7 diiodo-8-hydroxy-quinoline) was given orally three times a day for seven days.

The alternate plans of therapy, employed from the eighth to the fourteenth day of treatment, when Diodoquin was not available, consisted in the administration of either carbarsone, 0.25 Gm. twice daily, or chiniofon, 1 Gm. three times a day.

Diodoquin, which is nontoxic, was preferred to the prolonged administration of carbarsone, which has all the toxic properties inherent in any arsenical. Carbarsone was preferred to chiniofon because of the irritant action of the latter on the wall of the bowel, resulting in increased diarrhea and abdominal discomfort in 36 per cent of those patients treated with it.

As the margin between the therapeutic and the toxic dose of emetine hydrochloride is narrow, all the patients were kept at complete rest in bed, except for bathroom privileges, for the entire period of administration of the drug and for the succeeding two days. This routine was enforced in the expectation of diminishing the toxic effect of emetine hydrochloride on the myocardium. Daily cardiac auscultation was performed, and the blood pressure was recorded five minutes before and thirty minutes after the administration of the drug. Together with the emetine hydrochloride, 0.010 Gm. of thiamine hydrochloride was given intramuscularly, in an attempt to counteract the cardiac effects of the emetine hydrochloride. A bland diet, low in residue, high in animal protein and low in carbohydrate, was given, as Hegner and Eskridge [12] have shown that this type of diet retards the multiplication of the endameba. If a liquid diet was given, it was changed as rapidly as possible to a bland diet.

The carriers, or so-called cyst passers, were treated by one of the previously described plans of therapy, modified by the administration of emetine hydrochloride for only three days. Although emetine hydrochloride is not universally used in treating carriers, we used it because various authorities (Craig,[18] Johnson [19]) state that invasion of tissue occurs in all cases. In our experience, 25 per cent of carriers, examined sigmoidoscopically, showed petechial scarring of the mucosa of the bowel, evidence of previous activity and invasion of tissue. It was our opinion, therefore, that carriers deserved the benefit of therapy with emetine hydrochloride.

If a patient continued to harbor E. histolytica after any of the previously mentioned plans of therapy, he was given a cleansing enema of 2 per cent sodium bicarbonate solution followed by a 200 cc. retention

enema of 2 per cent carbarsone in 2 per cent sodium bicarbonate solution for five consecutive mornings.

Table 11 lists the patients treated by each of the previously mentioned plans of therapy. Emetine and two courses of carbarsone were given to 252, or 54.3 per cent, of the patients: emetine, carbarsone and Diodoquin to 174, or 37.6 per cent; emetine, carbarsone and chiniofon to 37, or 7.9 per cent, and carbarsone alone to 1, or 0.8 per cent.

TABLE 11.—*Patients Treated by Each Plan of Therapy*

Type of Patient	Emetine Hydrochloride Carbarsone		Emetine Hydrochloride Carbarsone Diodoquin		Emetine Hydrochloride Carbarsone Chiniofon	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
With acute amebiasis..........	119	52.4	90	39.4	19	8.2
With chronic amebiasis........	29	48.4	25	41.6	6	10.0
Carriers *	72	59.5	44	36.4	4	3.3
With mixed infections (amebic and bacillary)..............	30	56.6	15	28.2	8	15.2
With hepatic abscess..........	2	100.0	0	0.0	0	0.0
Total......................	252	54.3	174	37.6	37	7.9

* One carrier (0.8 per cent) received carbarsone alone.

TABLE 12.—*Unsatisfactory Results of Therapy*

Result	Emetine Hydrochloride Carbarsone		Emetine Hydrochloride Carbarsone Diodoquin		Emetine Hydrochloride Carbarsone Chiniofon		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total number of patients..	252	54.4	174	37.6	37	8.1	463	100.0
Stool contained organism after one course; patient cured by second course.........	4	1.5	1	0.5	0	0.0	5	1.08
Recurrence of disease after patient had been discharged is cured by second course	4	1.5	1	0.5	0	0.0	5	1.08
Patient returned to United States	1	0.4	3	1.7	1	2.7	5	1.08
Patient persistently infected	0	0.4	0	0.0	0	0.0	1	0.22
Patient had chronic colitis..	0	0.0	3	1.7	1	2.7	4	0.86
Total...................	9	3.4	5	2.7	1	2.7	15	3.23

Table 12 lists those patients who, in our opinion, did not respond satisfactorily to a single course of therapy. Of all the patients treated, 15, or 3.3 per cent, fell into this category. Of those treated with emetine hydrochloride and two courses of carbarsone, 5, or 1.9 per cent, continued to pass E. histolytica after the completion of therapy. Four of these 5 cleared after a second course of therapy. The fifth patient continued to pass E. histolytica after two courses of emetine hydrochloride and carbarsone followed by retention enemas. This patient,

who proved refractory to treatment and was evacuated to the Zone of the Interior, had originally been given a diagnosis and treated in Mexico three years prior to admission and had subsequently received several courses of therapy in the United States. Of those treated with emetine, carbarsone and Diodoquin, 1, or 0.57 per cent, continued to pass E. histolytica after one course of therapy, while 3, or 1.7 per cent, continued to have abdominal symptoms and, after two courses of therapy, were evacuated to the Zone of the Interior with a diagnosis of chronic colitis, manifested by persistent loose stools, abdominal discomfort, confirmatory sigmoidoscopic findings and repeatedly negative results of stool examinations for E. histolytica or pathogenic enteric organisms. Of those treated with emetine hydrochloride, carbarsone and chiniofon, none continued to pass E. histolytica after the initial course of therapy, but 1, or 2.7 per cent, experienced chronic colitis and was evacuated to the Zone of the Interior.

A second group of patients who must be considered in evaluating the results of therapy are those in whom symptoms again developed and who again began to pass E. histolytica in the feces within one month of their discharge from the hospital. It is impossible to determine whether these were patients who were reinfested following their discharge from the hospital or whether they had continued to harbor E. histolytica. We feel that the latter supposition is the more correct one, and it will be so considered in this report. Of those treated with emetine hydrochloride and two courses of carbarsone, 4, or 1.5 per cent, were in the second category, and of those treated with emetine hydrochloride, carbarsone and Diodoquin, 1, or 0.57 per cent, was readmitted.

Thus 9, or 3.9 per cent, of those treated with emetine and two courses of carbarsone, 5, or 2.8 per cent, of those treated with emetine hydrochloride, carbarsone and Diodoquin and 1, or 2.7 per cent of those treated with emetine hydrochloride, carbarsone and chiniofon (a total of 15, or 3.3 per cent of all patients) failed to respond satisfactorily to a single course of therapy. A total of 5, or 1.05 per cent, of the patients were evacuated to the Zone of the Interior, 1 being totally refractory to therapy and the other 4 because of the development of a chronic colitis. It is interesting to note that these 4 patients all had contributory psychogenic factors complicating the clinical picture.

Nineteen, or 4.1 per cent, of the patients, 17 of whom presented a severe clinical picture at the time of admission, continued to have loose stools with vague abdominal distress and slight erythema of the wall of the bowel with stools persistently negative for E. histolytica or for pathogenic enteric organisms after the completion of therapy. It was felt that the ulcerations and other damage caused by the previous action of the amebas had not had sufficient time to heal. These patients were given 8 Gm. of kaolin, 0.6 cc. of tincture of opium and 1 Gm. of

calcium gluconate twice daily for five days. Following this, the symptoms subsided entirely and the wall of the bowel appeared normal.

Using the previously outlined methods of treatment, reactions which were attributable to emetine hydrochloride were encountered in 27, or 5.7 per cent, of the patients. Precordial distress, mild in nature, occurring on the third or fourth day, developed in 15, or 3.2 per cent, of the patients. Increasing diarrhea, occurring on the third or fourth day, developed in 3, or 0.3 per cent of the patients. Three patients were treated for mitral stenosis. In 1 patient the murmur increased in intensity on the third day and the heart sounds of the second became faint on the fourth day, while no change was noted in the third patient during the entire period of emetine hydrochloride therapy. Sterile abscesses at the site of injection developed in 4, or 0.9 per cent, of the patients. Extrasystoles occurred in 1, or 0.2 per cent, of the patients, while neuritis developed in 2, or 0.4 per cent, of the patients. All the patients complained of local pain at the site of the injection; this pain persisted for three to four days after the injection. There were no patients who experienced any pronounced drop in blood pressure. No permanent residual effects were encountered.

Of those patients receiving chiniofon, 13, or 26 per cent, experienced moderate diarrhea and abdominal discomfort after three or four days' administration of the drug. For this reason, the routine use of chiniofon was discontinued.

Because of military limitations, it was possible to perform satisfactory follow-up examinations only on the members of the hospital personnel. Of the 166 members of the hospital staff treated, all except 3, or 1.7 per cent, have remained persistently free of the infection. These 3 were readmitted for a second course of therapy, following which they also have remained free of the infection.

Under the plan of therapy outlined in this article, the patients with acute amebiasis have had an average hospitalization of 20.6 days; the patients with chronic amebiasis, 24.6 days; the carriers, 18.4 days, and the patients with mixed infections, 24 days. One of the patients with hepatic abscess was hospitalized 57 days and the other 45 days. The average period of hospitalization for the entaire series was 20.9 days.

COMMENTS

An attempt has been made to present our experience in the diagnosis and treatment of amebiasis in the American armed forces in the Middle East. This disease is of importance not only to the military medical officer but to the civilian physician as well. American troops will return to the continental limits of the United States from many areas in which amebiasis is prevalent. Since the virulence of the organism is said to differ in various localities and since the disease in

any given endemic region affects the native population and the "foreigner" in a different manner, a report of the reactions of American troops to infection with E. histolytica should be compiled for each area in which the disease is prevalent.

We are in hearty agreement with the use of the term "amebiasis" rather than the term "amebic dysentery." The majority of the patients in this series had little or no diarrhea, nor did they have a dysenteric stool. The infection was, in general, a mild one. It is felt that the disease must be suspected in every one who has resided in an endemic area, particularly if there is a history of intermittent loose stools alternating with normal stools, mild intermittent abdominal pain, fatigability and vague psychosomatic complaints, among which are irritability, restlessness and gastrointestinal dysfunction.

SUMMARY

1. This report extends from November 1942 to November 1944, inclusive, and describes the experience of an American army hospital, located in the Middle East, with respect to 464 cases of amebiasis.

2. Monthly examinations of purged stools of the mess personnel of the hospital revealed that 36.4 per cent acquired infection with E. histolytica during the two year period.

3. Ninety per cent of the native workmen examined had one or more pathogenic organisms in their feces. Twenty-two per cent had E. histolytica.

4. At the time of admission, 26.5 per cent of the patients were asymptomatic; 35.7 per cent had mild symptoms; 24.4 per cent had moderate symptoms, and 13.4 per cent had severe symptoms.

5. Of the patients 41.8 per cent had no diarrhea at the time of admission; 33.8 per cent had loose stools, and 24.4 per cent had diarrhea.

6. Of the patients 57.5 per cent had abdominal pain; 40.2 per cent had abdominal tenderness; 15.6 per cent had an elevation of temperature and 11.9 per cent had an abnormally large number of leukocytes at the time of admission.

7. Of the patients with acute amebiasis 18.1 per cent had a dysenteric stool, and of the patients with chronic amebiasis, 16.7 per cent.

8. Of those examined sigmoidoscopically, 10.1 per cent of the patients with acute amebiasis, 10.2 per cent of the patients with chronic amebiasis and 75 per cent of the carriers had a normal-appearing wall of the bowel.

9. There was amebic involvement in 3.2 per cent of the appendectomies performed during the period covered by this report.

10. The average period of hospitalization was 20.9 days.

THROMBOANGIITIS OF PULMONARY VESSELS ASSOCIATED WITH ANEURYSM OF PULMONARY ARTERY

Report of a Case

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ANEURYSM of the pulmonary artery is a type of lesion encountered infrequently. Boyd and McGavack [1] reviewed the literature from 1833 to 1939 and reported 139 cases. Additional ones have been published by Hartwell and Tilden,[2] by Thompson [3] and by Breslin, Solway and Eisen.[4]

This paper reports a case in which an aneurysm of the right pulmonary artery of more than 10 cm. in diameter developed within a period of three months and was associated with thromboangiitis of both pulmonary arteries and veins.

REPORT OF CASE.

The patient, a white man 27 years old, was inducted into the United States Army in the spring of 1941 but was discharged two months later because of a perforated ear drum. During his short stay in the army he had two attacks of "influenza." On Jan. 11, 1942 he was treated at the Waterbury Hospital in Connecticut for an acute gonorrheal prostatitis.

On March 19, 1942 he was admitted to St. Mary's Hospital in Waterbury with severe pain in the left side of the chest and with a temperature varying from 100 to 104.6 F. A roentgenogram of the chest (fig. 1) showed a rounded area of increased density in the periphery of the left lung at the level of the third anterior interspace. It also disclosed a smaller lesion of fainter density about 1.5 cm. in diameter at the extreme base of the lung on the right side. A blood count revealed: red blood cells, 4,000,000; hemoglobin content, 78 per cent; white blood cells, 8,000, with polymorphonuclear leukocytes 68 per cent, small

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3. Thompson, S. A.: Differential Diagnosis by Means of Intravenous Contrast Medium of Two Cases Simulating Aneurysm of Pulmonary Artery, Am. J. Roentgenol. **46**:646, 1941.

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Figs. 1, 2, 3, 4, 5 and 6.—Roentgenograms of the chest. Figure 1 was taken on March 19, 1942; figure 2, on Nov. 27, 1943; figure 3, on Jan. 3, 1944; figure 4, on March 1, 1944; figure 5 (lateral view), on March 1, 1944, and figure 6, on April 21, 1944.

lymphocytes 10 per cent, monocytes 20 per cent and eosinophils 2 per cent. An agglutination test for typhoid H on March 28, 1942 elicited 3 plus reaction in dilution of 1:80, 2 plus in dilution of 1:160 and 1 plus in dilution of 1:320. This test was repeated on April 6 with the same results. No typhoid organisms, however, were recovered from either feces or urine. The patient's temperature remained elevated for two weeks, reaching 104.6 F. during the first four days and then gradually dropping to 100.6 F. by the end of fourteen days. Severe pain in the left side of the chest and in the legs and arms together with chills and a nonproductive cough persisted through the first two weeks. Reddened areas, macular in type, developed, first on the arms and legs and gradually spread over the body. For the first nine days the patient received sulfadiazine. His symptoms abated, although he still complained of occasional pain in the left side of the chest and of a cough. The roentgenograms were not repeated. The patient was discharged on April 15, 1942 with the impression that he had had typhoid.

Following his discharge the patient remained comparatively well, although he did have three or four attacks of "influenza."

He was readmitted to the Waterbury Hospital on Dec. 6, 1942 for a left epididymectomy. His temperature rose to 104.2 F., and he had severe chills during his postoperative course. He was given sulfanilamide, and by the end of four days his temperature was normal. The excised epididymis was reported to have shown round cell infiltration with no evidence of tuberculosis.

The patient contracted a "cold" about Nov. 1, 1943. In a few days this was followed by a sudden chill succeeded by a rise in temperature to 104 F. He also began to complain of severe and continuous pain in his entire chest. This was accompanied with a constant irritating cough. The sputum contained small amounts of blood. He was treated at home by a physician who diagnosed his disease as pneumonia of the left lung. During this period his temperature was from 103 F. to 104 F.

Because the patient showed no improvement, he was readmitted to St. Mary's Hospital on November 26. Examination on admission disclosed many rales in the lower lobe of the left lung, without evidence of consolidation. The results of urinalysis were normal. Examination of the blood showed 4,380,000 red blood cells, a hemoglobin content of 81 per cent and 16,100 white blood cells with polymorphocytes 88 per cent and lymphocytes 12 per cent. During the first four weeks of his hospitalization he was febrile, the number of white blood cells remained higher than normal, and there was a gradual decrease in the number of red blood cells, reaching a low of 3,550,000. Cultures of blood were sterile. Examination of the sputum for the bacilli of tuberculosis and for pneumococci gave negative results. The patient's temperature began to drop slowly beginning in the early part of December 1943. He was treated symptomatically and was also given a course of sulfadiazine. A roentgenogram of the chest on Nov. 27, 1943 (fig. 2) was interpreted as revealing pneumonia of the left lung with fluid in the left pleural cavity. A roentgenogram of the chest on Jan. 3, 1944 (fig. 3) revealed both a diaphragmatic pleurisy on the left side with the diaphragm about 5 cm. higher on the left than on the right side and an infiltration of the middle of the left pulmonary field. There was a small oval area of increased density at the base of the right lung with some denseness about the right hilus. The patient left the hospital against the advice of his physician on January 12.

On Feb. 26, 1944 he had hemoptysis with chills, fever and severe pain in the right side of the chest. He was readmitted to the Waterbury Hospital on March 1. On admission his temperature was 103.4 F., his pulse rate 120 and his respiration rate 30. Examination of the chest revealed moist rales, increased breath sounds

and decreased vocal and tactile fremitus over the right lung posteriorly from the angle of the scapula to the base. There was a friction rub on the right side anteriorly at the fourth interspace. The patient was immediately ·given sulfadiazine, with which he seemed to make slight progress. Shortly after the patient's admission cyanosis developed and he was put into an oxygen tent. He rebelled against this and was removed after twenty-four hours. He continued to complain of severe pain in the right side of the chest and of a constant irritating cough productive of blood-streaked sputum. His temperature remained elevated throughout his hospitalization.

A roentgenogram taken on admission (fig. 4) showed that the left side of the diaphragm was partially obscured. There was a dense area measuring 10 cm. in its greatest diameter below the third rib on the right anteriorly, confluent with the hilus and obscuring the right side of the heart. A lateral view (fig. 5) located the density in the anterior portion of the chest. A roentgenogram on March 9 disclosed an increase of this density. The impression was that he had pneumonia with encapsulated fluid in the lower anterior part of the right side of the chest. On examination of the blood, the red cell count was indicative of a moderate secondary anemia. There were 10,600 white cells with a normal differential count. The blood chemistry and urine were normal. The blood pressure was 132 systolic and 76 diastolic. Examinations of sputum for acid-fast bacilli were unsuccessful. Cultures of sputum and of blood were also negative for hemolytic streptococci and for pneumococci. The electrocardiogram was normal. On March 11, 1944 about 300 cc. of straw-colored, slightly bloody fluid was obtained from the right side of his chest, and this fluid was negative for acid-fast organisms. On April 7 the patient had a moderately severe hemoptysis. He was given two blood transfusions of 500 cc. each.

On April 20, 1944 the patient was transferred to the Undercliff Sanatorium in Meriden, Conn. His symptoms were as before. The temperature was 100 F., the pulse rate 112 and the respiration rate 30. Physical examination of the chest revealed normal breath sounds on the right side down to the third rib anteriorly. There were flatness and absence of breath sounds from the third rib anteriorly to the base of the lung. The breath sounds were well heard throughout posteriorly. Pulsation and murmurs were not noted. Hyperresonance with increased breath sound·was found in the upper two thirds of the chest on the left side anteriorly. The lower third showed diminished breath sounds and impairment of the percussion note. Posteriorly, the conditions observed were normal. Heart sounds were regular, weak and rapid, but no murmurs were heard. The patient's condition continued to be critical. An attempt at thoracentesis on May 1, 1944 was unsuccessful, with only a small amount of pure blood being obtained. His sputum was persistently streaked with blood. The erythrocyte sedimentation rate was 62 per cent (31 per cent by the Cutler method). The urine was normal, and the Mazzini test elicited a negative reaction.

A stereoscopic roentgenologic examination of the chest on April 21, 1944 (fig. 6) revealed on the right side a mass occupying the lower half of the chest. The upper border was well defined, but the lower limits were less clearly outlined. This shadow extended to the base of the lung, except for a small area in the costophrenic angle. It seemed to extend beyond the spine in the midline. Above this area the lung appeared to be free of disease. On the left there was pronounced peaking of the diaphragm, with an area of increased but poorly defined density extending from the sixth to the eighth ribs posteriorly in all zones. This area was not as dense as that which was seen on the opposite side and appeared to be a faint haze rather than a definite density of the parenchyma.

On May 27, 1944 the patient died about five minutes after raising 240 cc. of blood.

Necropsy.—Gross Observations: The body was that of a well developed but extremely emaciated white man, 27 years old, measuring 167 cm. in length and weighing approximately 50 Kg. The skin was pale. Both pupils were round, and they measured 4 and 3 mm. for the left and right, respectively. Bloody foamy fluid exuded from the nares and the mouth. No enlarged lymph nodes were palpable in the supraclavicular and axillary fossae or in the groin. The finger tips were slightly cyanotic but not clubbed. Edema was absent. On the right the scrotum was of usual appearance. A small linear longitudinal scar was found over the left side of the scrotum. The left epididymis was absent. The left testicle, however, was similar to the right one. The abdominal organs occupied their usual position. No excess fluid was present in the abdominal cavity, and the peritoneum was intact.

On removal of the chest plate, numerous fibrous adhesions were encountered, binding the anterior surface of the right lung to the chest plate. Only the upper part of the pleural space on the right side was patent. The pleural space on the left side was patent, with a few delicate fibrous adhesions extending between the visceral and the parietal pleura. The pericardial sac was partly covered by the left lung. The sac contained 30 cc. of a clear yellow fluid. Its lining was intact. The pulmonary artery contained fluid blood when it was incised at its origin.

Heart. The heart was the usual size and shape and weighed 270 Gm. The epicardium was intact. On incision, the musculature was a pale brownish color. The entire endocardium was smooth and glistening. The coronary ostia as well as the coronary arteries were patent. There was no evidence of hypertrophy or dilatation of either ventricle. The ductus arteriosus was obliterated. The aorta did not show any syphilitic lesions.

Lungs. The left lung, on removal, was largely air containing but slightly more resistant than is usual. The pleura revealed many small areas of dark red discoloration. The cut surface of the lower and upper lobes showed numerous lobules containing a hemorrhagic exudate. There were also several star-shaped areas of fibrosis in both the upper and the lower lobes. The largest one, measuring 6 by 8 mm., was found in the lateral segment of the lower lobe. No fresh infarcts were apparent on gross inspection. The left branch of the pulmonary artery, as seen on its cut surface near the hilus, was distended to a diameter of 2.5 cm. and contained a clot which was grayish red for about two thirds of its cut surface and dark red for the remaining third. Two bronchial lumens containing some clotted blood were found close to the posterior circumference of the vessel. The thrombus extended for about 2 cm. into the branch of the artery serving the upper lobe (fig. 7) but no thrombosed vessel could be found in the central or peripheral segments of the left lung.

The middle lobe of the right lung was displaced by a globelike structure with a firm capsule of grayish dark-purple color. It had dislocated the lower lobe posteriorly and laterally. On removal and incision, the lesion (fig. 8) measured 12 cm. in diameter and was largely occluded by a laminated clot of blood. Only a small tangential segment of the upper anterior lobe contained fluid blood. The part of the capsule adjacent to the hilus differed from the peripheral parts in its yellowish white color and in its firm structure. The compressed and atelectatic parenchyma of the middle lobe was found at the upper circumference of the lesion. Two large vessels (fig. 9) were located medially from its upper pole. The one situated cranially was rather thin-walled and measured 3 cm. in diameter. Two thirds of its lumen was occluded by a laminated purplish gray thrombus,

while the blood clot occupying the rest of the lumen seemed to be a postmortem formation. A bronchial lumen was noted at the upper circumference of this vessel. A second vessel was located between the large one just described and
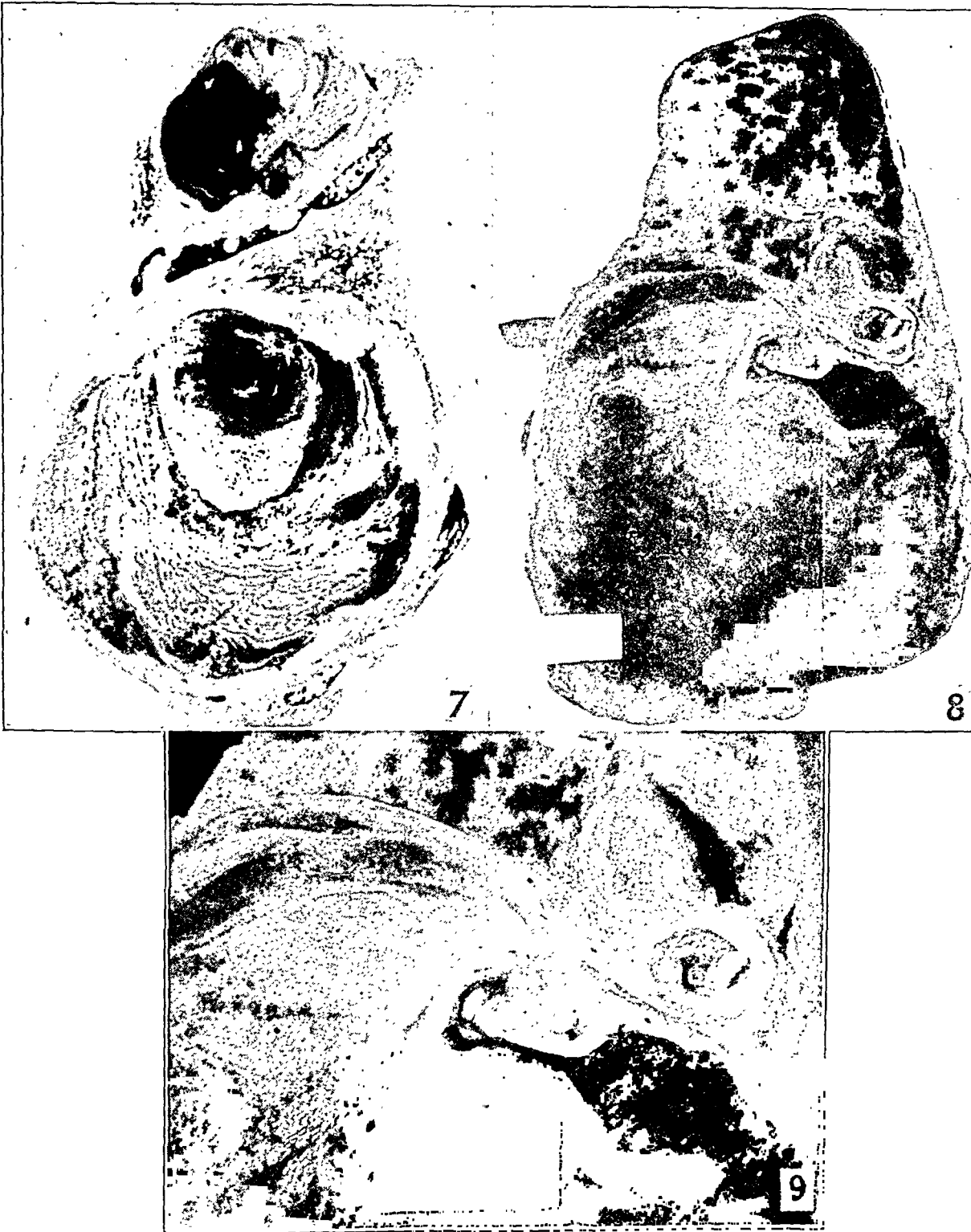
Figs. 7, 8 and 9.—Figure 7 shows vessels from the hilus of the left lung (hematoxylin and eosin stain; × 2). Figure 8 shows the right lung. Figure 9 shows a close-up view of the right hilus and the upper pole of the aneurysm.

the wall of the globe-shaped aneurysm. The wall of this second vessel was grayish yellow and firm and measured 1 to 2 mm. in diameter. More than half of its lumen was occupied by an antemortem thrombus. Some compressed pulmonary parenchyma could be seen interposed between the vessel and the wall of the aneurysm. The cut surfaces of the upper and the lower lobe of the right lung showed numerous alveoli filled with aspirated blood. Small star-shaped areas of fibrosis were found in the upper lobe, but no changes in the vessels could be ascertained.

Fig. 10.—Wall of the right pulmonary artery (hematoxylin and eosin; × 100).

Study of the other organs failed to reveal any changes. There was no indication of passive congestion of the liver.

Microscopic Observations: Sections from the left lung revealed small fresh infarcts as well as organized ones in addition to numerous alveoli containing well preserved red blood cells. Several small arteries were occluded by organized and recanalized thrombi. Microscopic study of the large hilar vessels revealed that about half of the lumen of the pulmonary artery was occluded by an antemortem clot with organization starting at its periphery. The media was largely

replaced by fibrous connective tissue (fig. 7), and small round cell infiltration of varying intensity was seen throughout the wall. The internal elastic membrane could not be identified with a Van Gieson elastic tissue stain. Remnants of the outer elastic lamina were seen in various parts of the wall.

The changes in the large pulmonary vessels on the right side were similar to those on the left. The thin-walled cranially located lumen mentioned in the gross observation was identified as that of a pulmonary vein. The wall of the artery located between the vein and the aneurysm showed the media preserved for about two thirds of the circumference. In the remaining third, the media was replaced by fibrous tissue that was densely infiltrated by small round cells (fig. 10). At one point, vacuolated monocytes and round cells had entirely replaced the media.

Figs. 11 and 12.—Wall of the aneurysm. In figure 11 Masson's stain was used (× 80); in figure 12, Van Gieson's stain for elastic tissue (× 300).

The wall of the aneurysm was composed of bundles of fibrous connective tissue that were usually densely arranged. At some points, however, the connective tissue fibers were spread apart by monocytes, many of which showed a foamy cytoplasm. A few smooth, parallel muscle fibers could be identified close to the hilus (fig. 11), while fragments of wavy elastic fibers were seen (fig. 12) in sections of peripheral segments of the wall of the aneurysm.

COMMENT

Several features of this case are of particular interest. The development of a large aneurysm in a period of three months and without signs of murmurs or palpitation may be explained by assuming that the force

of the flow of blood, while sufficient to expand the damaged arterial wall, engendered such velocity that the physical signs usually associated with saccular aneurysm were not produced.

When the cause of the changes of the pulmonary vessels in this case is considered, rheumatic fever, Streptococcus viridans infection, syphilis and congenital malformation as reported by others [1] seem to be excluded by the clinical course and by the laboratory and necropsy observations.

The history of this patient reveals that he had contracted several infectious diseases. The first, gonorrhea, is unlikely to have furnished the etiologic agent. A gonococcic septicemia would most likely have produced a fulminating endocarditis with valvular involvement. The absence of the latter speaks against the assumption of a gonococcic septicemia. The second disease, diagnosed as typhoid, cannot in retrospect be considered as established, because the organisms were not recovered from the blood, urine or feces and the agglutinin titer did not rise on subsequent tests.

The pulmonary lesions found by roentgenologic examination during the first week of the patient's second illness are not characteristic of infarcts, and the occurrence of thrombophlebitis and subsequent embolism during the first week of typhoid would be unlikely. Unfortunately, this part of the patient's history became known only some time after death. It could not be ascertained whether the patient had been immunized against typhoid during his stay in the army.

It has been suggested that the conditions described herein may represent a variety of periarteritis nodosa. In 1942 there were pains in the extremities, a macular rash and patchy pulmonary infiltrations, compatible with a pulmonary form of periarteritis.[5] The fact that elevation of eosinophils in the blood was not present in this case does not necessarily exclude the possibility of periarteritis nodosa.[6]

The lesions of the smaller vessels might represent healed stages of periarteritis, although no local polymorphonuclear or eosinophilic infiltrations were observed in the recent lesions of the pulmonary vessel. Such observations were once made.[7] Should this case report be interpreted as an instance of the disease, the unusual involvement of the larger pulmonary vessels would add a new feature to the already complex syndrome of periarteritis.

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ACUTE PORPHYRIA

I. Investigations on the Pathology of the Porphyrins and Identification of the Excretion of Uroporphyrin I

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IT IS now well recognized that porphyria (so-called hematoporphyrinuria [Garrod,[1] 1923]) is a condition characterized by two main clinical types, the acute iodiopathic and the congenital, each possessing its characteristic symptomatology. In addition, there is recognized a toxic type due to various drugs, such as sulfonmethane, trinitrotoluene and sulfonamide compounds (Rimington and Hemmings,[2] 1939) which resembles clinically the acute idiopathic form. The classic case of congenital porphyria, studied in detail from the chemical and histochemical aspects by Fischer and his school and by Borst and Königsdörffer[3] (1929), was that of the man Petry. This work established a pathologic excretion of coproporphyrin in urine and feces, together with the appearance of pathologic porphyrin and uroporphyrin in the urine. These porphyrins were in the main type I porphyrin isomers, in contrast to the physiologically occurring type III protoporphyrin of the blood. Rimington[4] (1936) carried out a detailed examination of a similar condition in South African cattle, with similar observations, the large depositions of uroporphyrin I in the bones being striking, as in the case of Petry.

Investigations into acute porphyria, which is relatively common in Sweden, has more recently been undertaken by Waldenström[5] (1937). The main observation was the occurrence of coproporphyrin and uroporphyrin, both considered to be type III isomers. On this basis it was becoming accepted that an excretion of type I porphyrin was characteristic of the congenital form and an excretion of type III of the acute idiopathic form of the disease (Chandler, Harrison and Rimington,[6] 1939). In addition, there was no evidence of abnormal

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1. Garrod, A. E.: Inborn Errors of Metabolism, ed. 2, London, Oxford University Press, 1923.

2. Rimington, C., and Hemmings, A. W.: Biochem. J. **33**:960, 1939.

3. Borst, M., and Königsdörffer, H., Jr.: Untersuchungen über Porphyrie mit besonderer Berücksichtigung der Porphyria congenita, Leipzig, S. Hirzel, 1929.

4. Rimington, C.: Onderstepoort J. Vet. Sc. **7**:567, 1936.

5. Waldenström, J.: Acta med. Scandinav., 1937, supp. 82, pp. 1-254.

6. Chandler, F. C.; Harrison, G. A., and Rimington, C.: Brit. M. J. **2**:1173, 1939.

deposition of porphyrin in the tissues in the acute form, in contrast to observations in the congenital type. Recently there has appeared a study of the question by Watson and his colleagues (Grinstein, Schwartz and Watson,[7] 1945; Watson, Schwartz and Hawkinson,[8] 1945), in which it has been suggested that the uroporphyrin of acute porphyria, the porphyrin which is in fact the outstanding pathologic product in these diseases, is a mixture of uroporphyrin type I with a small amount of a type III compound isolated as a heptamethyl ester, and not an octamethyl ester, which is characteristic of uroporphyrin. Further contributions have been the finding for the first time of uroporphyrin in the liver and the feces.

Chandler, Harrison and Rimington [6] (1939) have pointed out that even today acute idiopathic porphyria is scarcely mentioned in the British literature. The present paper records the detailed investigation of another case which came to autopsy and brought to light a second case, an example of the "latent" form of the disease. The investigations reported in this paper were well advanced before the appearance of Watson's recent work mentioned previously, but this has stimulated their extension.

The remarks in the foregoing paragraphs give only a brief outline of the position. For extensive reviews the reader should consult publications by Mason, Courville and Ziskind [9] (1933), Vannotti [10] (1927), Watson [11] (1938), Dobriner and Rhoads [12] (1940), Turner [13] (1940), Nesbitt [14] (1944) and Welcker [15] (1945), in which a complete bibliography can be found.

REPORT OF A CASE .

First Attack.—A girl aged 16, a domestic worker, complained of an attack of acute abdominal pain for six days, accompanied with vomiting and constipation. Her history revealed that she had been a premature baby with the remarkable birth weight of 14 ounces (397 Gm.), but after attaining 5 pounds (2.3 Kg.) at 4½ months she subsequently developed normally, apart from some kyphotic deformity, for which she received treatment, and rather subnormal intelligence. She had scarlet fever at the age of 8 years and a tonsillectomy at 11 years. Two

7. Grinstein, M.; Schwartz, S., and Watson, C. J.: J. Biol. Chem. **157**:323, 1945.

8. Watson, C. J.; Schwartz, S., and Hawkinson, V.: J. Biol. Chem. **157**: 345, 1945.

9. Mason, V. R.; Courville, C. B., and Ziskind, E.: Medicine **12**:355, 1933.

10. Vannotti, A.: Porphyrine und Porphyrinkrankheiten, Berlin, Julius Springer, 1937.

11. Watson, C. J., in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1938, vol. 4, p. 228.

12. Dobriner, K., and Rhoads, C. P.: Physiol. Rev. **20**:416, 1940.

13. Turner, W. J.: J. Lab. & Clin. Med **26**:323, 1940

14. Nesbitt, S.: Acute Porphyria, J. A. M. A. **124**:286 (Jan. 29) 1944.

15. Welcker, M. L.: New England J. Med. **232**:11, 1945.

months before being seen she had a generalized rash, diagnosed as psoriasis, and this had disappeared within a month. There was no history of photosensitivity or of recent ingestion of any drugs.

On admission, on May 6, the patient had been having convulsions for the previous four hours, and there were two epileptiform attacks, with incontinence, in the wards. The plantar responses were extensor. The temperature was 101.5 F. and the pulse rate 140. Lumbar puncture demonstrated nothing abnormal. The following day the patient was restless and uncooperative but complained of pain in the abdomen, mainly in the right iliac fossa. She said that it was burning in character and relieved by heat and raising the legs. Examination revealed a thin person with an external strabisums. She was menstruating. The temperature was 100.5 F. and the pulse rate 110. The tongue was furred but moist. There was tenderness on deep pressure in the right iliac fossa with guarding but no localized signs or hyperesthesia. Neither the liver nor the spleen was palpable. Catheterization gave a urine containing a trace of albumin, a few leukocytes and red blood cells and a moderate number of hyaline and granular casts. The blood pressure was 120 systolic and 80 diastolic.

Three days later the urine was noticed to darken on standing. The abdominal pain had slightly improved and ten days after admission had disappeared. She remained febrile with the temperature up to 99 F., for four weeks. Constipation was pronounced. A chart of the pulse rate is shown in figure 4. After six weeks she was discharged, symptom free.

Investigations.—On May 9 the urine contained a trace of albumin, a few leukocytes and red blood cells and a moderate number of granular and hyaline casts.

Spectroscopic examination revealed absorption bands at approximately 575 and 540 millimicrons, with a broad band extending to the right of 510 millimicrons due to a porphyrin-metal complex. Acidification to 1 per cent with hydrochloric acid produced the bands at 597 and 550 millimicrons of the acid porphyrin spectrum. The urine exhibited red fluorescence in ultraviolet rays. A diagnosis of acute porphyria was thus established.

On May 10 the leukocytes numbered 16,500, of which 74 per cent were polymorphonculear. The urine was found to contain large quantities of coproporphyrin and uroporphyrin. Details of the examination are given subsequently. The cerebrospinal fluid and plasma gave no fluorescence or spectroscopic evidence of the presence of porphyrin.

On May 15 a hematologic examination showed 5,620,000 red blood cells and a hemoglobin level of 100 per cent (Haldane).

On May 22 the blood urea level was 43 mg. per hundred cubic centimeters; plasma protein level 7.5 mg, and albumin level 3.4 mg. The icteric index was 5. The van den Bergh test elicited a negative reaction (direct). A hippuric acid synthesis test revealed 77 per cent normal function. The Schlesinger test elicited a 2 plus reaction for urobilin in the urine.

On May 23 a test for sensitivity to ultraviolet rays was carried out; an exposure of thirty seconds to an erythema dose produced no response. The patient then spent several days exposed to bright sunshine without effect.

On May 24 the number of leukocytes was 4,800; on May 30 the number was 6,100, and on June 6 it was 6,500.

Second Attack.—On December 7, the patient was again admitted to the hospital, complaining of abdominal pain and vomiting for five days. The pain was described as a continual dull ache in the umbilical region, relieved by heat. She was emotionally very unstable. The abdominal physical signs resembled

those previously noted, and the descending colon was loaded with feces. There was no oliguria. The temperature was 99.5 F. and the pulse rate 100. The pulse rate and temperature continued to rise throughout the subsequent course of the attack. The blood pressure was 150, systolic and 110 diastolic. The patient was very constipated.

On December 11 menstruation commenced, and the abdominal pain was increasing. On December 13 the patient became incontinent and catheterization was resorted to, but it was later abandoned because of the risk of infection. The incontinence varied in severity during the remainder of the attack. By December 15 there was some symptomatic improvement, but on December 21 an ascending paralysis commenced, being first manifested by loss of power in the limbs. Tendon reflexes disappeared, but there was no sensory disturbance The next day bronchopneumonia was evident, and on December 23 intercostal paralysis appeared. The patient died on December 25.

Investigations.—On December 22 a hematologic examination showed 26,000 leukocytes, with 87 per cent polymorphonuclear leukocytes, 5,000,000 red cells and a hemglobin level of 94 per cent (Haldane). The urine contained no albumin, but there was an occasional granular cast. The chemical examination of the blood showed: urea, 62 mg. per hundred cubic centimeters; plasma protein, 6.5 mg., and albumin, 3.2 mg. A slight increase of urobilin in the urine was found on only one occasion.

Fig. 1.—Relation of cases reported. (*d*, deceased at time of inquiry, age in brackets; *S*, stillborn; *L*, latent porphyrin; *P*, acute porphyrin; *X*, 16 relatives of patient's father examined with no abnormalities found. Dotted square and dotted circle indicate that urine was not examined.)

Treatment.—During the first attack the treatment was symptomatic. Belladonna produced no relief, the only effective drug being phenobarbital sodium. In the second attack supportive measures were instituted, but atropine and demerol (Pethidine [1-methyl-4-phenyl piperidine-4-carbonic acid]) were without effect. Again the minimal amount of pentobarbital sodium alternated with nepenthe was given. On December 11 1 Gm. of methionine was given daily and continued until December 21. On December 20 she was given Adexolin capsules (12,000 international units of vitiamin A and 2,000 units of vitamin D per cubic centimeter) and ascorbic acid.

Family History.—There was no history directly obtainable that any member of the family had suffered from porphyria. The patient's mother was said to be subject to "fits," but there was a coincidental history of hypertension. The maternal grandmother died at the age of 42, but the cause of death could not be elucidated. Morning specimens of urine from as many members of the family as possible were examined, with the results shown in figure 1. Of the persons examined, only 1, the patient's aunt, showed any evidence of latent

porphyria.[16] Of 27 members of the father's family included in three generations, the urine of 16 was examined and was normal.

Postmortem Examination.—The body was that of a well nourished girl of normal development. There was no hypertrichosis or pathologic pigmentation. The lips were deeply cyanosed.

Both lungs showed pneumonic consolidation in the lower lobes, particularly on the right. There were numerous small subpleural petechiae, and there was a small clear effusion in the right pleural cavity.

The heart weighed 9¼ ounces (262 Gm.) and appeared to have slight hypertrophy of the left ventricle. The pericardium contained a little clear fluid.

There was a small thymic remnant present. The intestinal tract appeared normal.

The liver weighed 40¾ ounces (1,155 Gm.) and had a well defined Reidel lobe. The capsule was thickened, and the cut surface showed a diffuse mottling, composed of pale areas, each approximately 2 by 2 mm. and pale gray. The color of the liver was considered remarkable, having a more definitely red appearance than normal. The spleen was about twice the normal size (weighing 5¾ ounces [162 Gm.]) and noticeably congested. The other abdominal organs appeared normal, except that the bladder contained 3 ounces (90 cc.) of pinkish urine. The uterus was of the infantile type. The brain (2½ pounds [1.1 Kg.]), spinal cord and peripheral nerves appeared normal to the naked eye. There was no apparent abnormality of the marrow removed from the upper part of the right femur and no macroscopic evidence of deposition of porphyrin in the bone.

Microscopic examination of the section of the organs stained with hematoxylin and eosin revealed no striking abnormalities, with the following exceptions: The liver showed slight thickening of Glisson's capsule, with a small degree of small round cell infiltration into it and the neighborhood of the portal areas. In the latter areas there was some fatty degeneration of the liver cells, also shown in frozen sections. The sinusoids showed some engorgement. In the center of many lobules were areas of liver cells in early stages of necrosis. This varied from cloudy swelling to swollen cells with coarsely granular cytoplasm and pyknotic nuclei. There was no infiltration of inflammatory cells into these zones, and the Kupffer cells were inconspicuous. Many of the liver cells showed deposits of granular pigment (fig. 6 *A*). These were to be found in the necrotic areas and also scattered through the liver substance. There were very few Kupffer cells containing these granules. The pigments appeared to be of two types: the first, golden yellow, large and small granules, and the second, small orange-red granules or diffuse patches of pigment throughout a portion of the cell. Sections stained for iron showed little indeed of this material to be present.

The kidneys showed some congestion of the glomerular capillaries, with swelling of the endothelial cells lining Bowman's capsule. In the tubules, particularly the convoluted tubules, were found pronounced degenerative changes with casts of epithelial debris. There appeared to be no pigment granules identifiable in the cells.

Sections of the central nervous system revealed no gross abnormalities, and some degree of postmortem change made the identification of minor degeneration difficult.

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16. The urine reacted weakly with paradimethylaminobenzaldehyde to give a red product insoluble in chloroform and with absorption bands at 570 to 555 and 525 millimicrons. The latter was extremely faint. The coproporphyrin content of the urine was estimated to be only 12.5 micrograms per liter, and no uroporphyrin could be detected.

Ultraviolet Microscopic Examination.—Liver: Among the cells laden with pigment granules previously described were clumps of pigment exhibiting a bright brownish red fluorescence. There were numerous areas of this type. The emission spectrum showed an intense bright band from 620 to 660 millimicrons. The brightest portion of the spectrum was in the neighborhood of 620 millimicrons.

Kidney: The tubules were lined with a ring of red fluorescence, which seemed most pronounced in the collecting tubules. There was also a diffuse reddish fluorescence among the necrotic epithelial elements contained in the tubules. The emission spectrum was continuous from 620 to 650 millimicrons, the brightest portion being at 620 millimicrons.

Costal Cartilage: Macroscopically there was present a red fluorescence in the central portion of the cut surface. Microscopically this appeared as a ring of red fluorescence immediately around the cartilage cells or alternately as small circumscribed globular zones of fluorescence adjacent to the cells. The emission spectrum ranged from 610 to 650 millimicrons, being brightest at 63 millimicrons.

The spinal cord, cerebellar cortex, cerebral cortex and pituitary gland, all showed minute pinkish orange fluorescent "droplets" scattered throughout the tissue. In the pituitary gland the effect was most noticeable in the posterior portion. There was insufficient fluorescence in any of these sections to identify the emission spectrum. Further work is in progress on the nature of this fluorescence.

The Excretion of Porphyrin.—Urine: The excretion of porphyrin in the urine was measured by the method of Rimington [17] (1943) a Hilger fluorometer with Chance No. 3 orange filter in the secondary beam being used. A solution of coproporphyrin, 0.5 microgram per cubic centimeter in 0.25 per cent hydrochloric acid, was used as a reference standard. The calibration curve (fig. 2) was almost identical with that of Rimington [17a] (1943), a different instrument being used. In the determination of total porphyrin by adsorption onto kieselguhr it was found impossible to remove all the residual blue fluorescence even when acetic acid washings were employed as advised by Rimington. This gave rise to the greatest trouble with low concentrations of uroporphyrin.

Feces: The fecal coproporphyrin was estimated in the earlier specimens by grinding 5 to 10 Gm. of wet feces with sufficient anhydrous sodium sulfate to bring the mixture to a dry powder. The powder was then moistened with about 3 cc. of glacial acetic acid and extracted with ether for three hours in a Soxhlet apparatus, when no more coproporphyrin was extracted. The ether extract was washed three times with water or 10 per cent sodium chloride if emulsions were difficult. Extraction of ether was carried out with 1 per cent hydrochloric acid until no more porphyrin was removed (fluoroscopic examination). The porphyrin was taken back to ether after the addition of solid sodium acetate and thence returned to 0.25 per cent hydrochloric acid. The last extract was washed with chloroform which removed a small amount of porphyrin. If the remaining hydrochloric acid extract was pigmented, it was taken back to ether and extracted again with 0.25 per cent hydrochloric acid. The final extract was made up to 50 cc. with 0.25 per cent hydrochloric acid and read in the fluorometer.

During the analysis of the feces obtained at necropsy, it was found that this method did not effect a complete extraction of the fecal coproporphyrin.

17. (a) Rimington, C., and Schuster, E.: Biochem. **37**:137, 1943. (b) Rimington, C.: ibid., **37**:443, 1943.
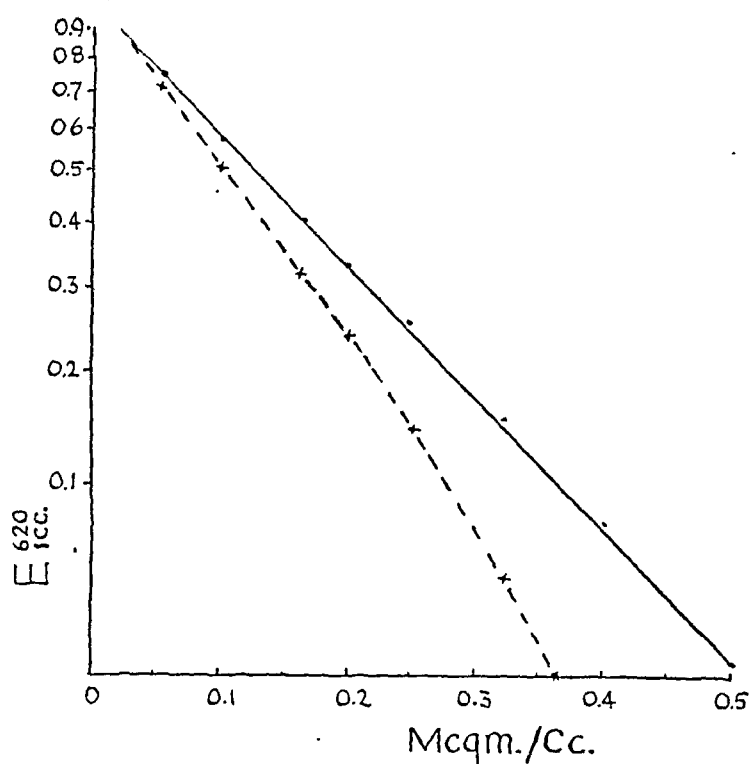
Fig. 2.—Calibration curve of porphyrin with Hilger fluorometer. (— —copro-porphyrin in 0.25 per cent hydrochloric acid; x - - - x—uroporphyrin in normal tenth sodium hydroxide.)
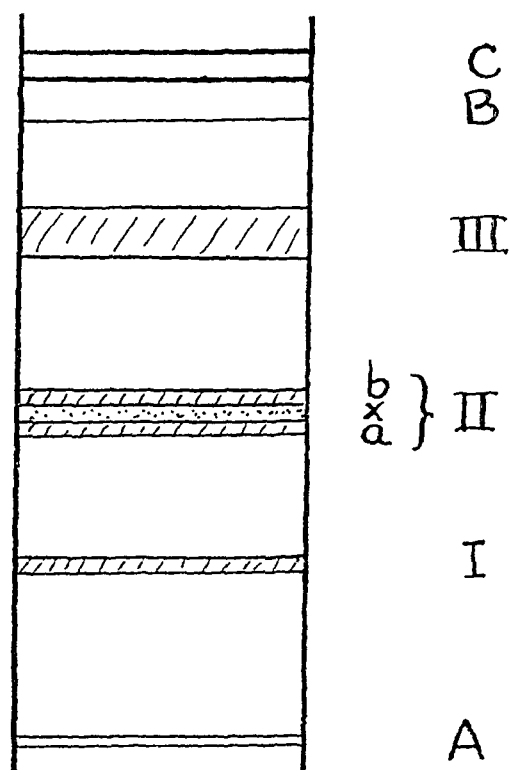
Fig. 3.—Composite diagram of the developed chromatogram of fecal extract. (Figures in brackets indicate ratio of chloroform: light liquid petrolatum in the solvent required for elution. *A*, yellow pigment [1 :10]; *I*, protoporphyrin [1 : 5]; *II*, porphyrin [1 : 4]; *III*, uroporphyrin [1 : 1]; *B*, yellowish green pigment; *C*, brown pigment.)

The residue from the extractions by the Soxhlet apparatus was treated with methyl alcohol, saturated with hydrochloric acid according to the technic of Schwartz and Watson [18] (1941). The extract was transferred to chloroform and adsorbed on an aluminum oxide column (Savory and Moore) from a mixture of 1 volume of chloroform and 10 volumes of light liquid petrolatum. Four porphyrin bands were developed under ultraviolet rays (fig. 3).

Another chromatogram of zone II was made on a new column, and bands *a* and *b* were obtained with better separation and free from the greenish pigment.[19] The solvent was evaporated off and the residue reesterified with methyl alcohol and hydrochloric acid. The absorption spectrums in chloroform were:

(*a*) 622; 580-562; 534; 490 millimicrons [18]
(*b*) 623; 582-560; 535; 500 millimicrons

The spectrum of *a* matched that of a pure coproporphyrin methyl ester. The dry coproporphyrin ester was saponified with 0.5 cc. of 25 per cent hydrochloric acid and the concentration diluted to 0.25 per cent and the porphyrin estimated fluorometrically (table 2).

The uroporphyrin (zone III) eluate was evaporated to dryness and neutralized with 10 per cent sodium hydroxide solution and diluted to 25 cc. with tenth-

TABEL 1.—*Corrections of Volumes of Urine for Incontinence*

Date, December	Urine Collected (Cc.)	Total Creatinine Obtained (Gm.)	Corrected Volume of 24 Hour Output (Cc.)
9	560 *	0.861	560
10	420 *	0.858	420
11	294	0.467	475
12	585 †	0.390	1,130
13	635 *	0.750	635
15	450 *	0.744	450
17	520	0.658	600
19	210	0.276	570
20	164	0.206	595
22	305	0.436	525

* A complete twenty-four hour collection.
† This specimen was contaminated with an unproductive saline enema. The patient was incontinent during this period.

normal sodium hydroxide solution. An aliquot diluted with tenth-normal sodium hydroxide solution was used for the fluorometric estimation of the uroporphyrin.

Porphobilinogen in the urine was estimated immediately at the termination of a twenty-four hour collection by the method of Waldenström and Vahlquist [20] (1939) a Hilger absorptiometer being used and 1 unit of porphobilinogen per cubic centimeter of solution being given by E 550 1 CM = 0.545, an Ilford 605 filter being used (maximum absorption at 550 millimicrons).

Corrections for Loss of Urine During Periods of Incontinence.—In order to assess the daily output of porphyrin and porphobilinogen during periods of incontinence the creatinine content of the specimens obtained during the twenty-

18. Schwartz, S., and Watson, C. J.: Proc. Soc. Exper. Biol. & Med. **47**: 390, 1941.

19. The fluorometric estimation of this fraction as "coproporphyrin" indicated 1,050 micrograms per hundred grams of wet feces (table 2).

20. Waldenström, J., and Vahlquist, B.: Ztschr. f. physiol. Chem. **259**: 213, 1939.

four hours was estimated, and the appropriate correction applied, assuming a 100 per cent collection to contain 0.75 Gm. of creatinine per twenty-four hours. Table 1 indicates these corrections.

Figure 4 shows the excretion of porphyrin and porphobilinogen in the urine during the first and second attacks respectively. Table 2 gives the excretion of porphyrin in the feces.
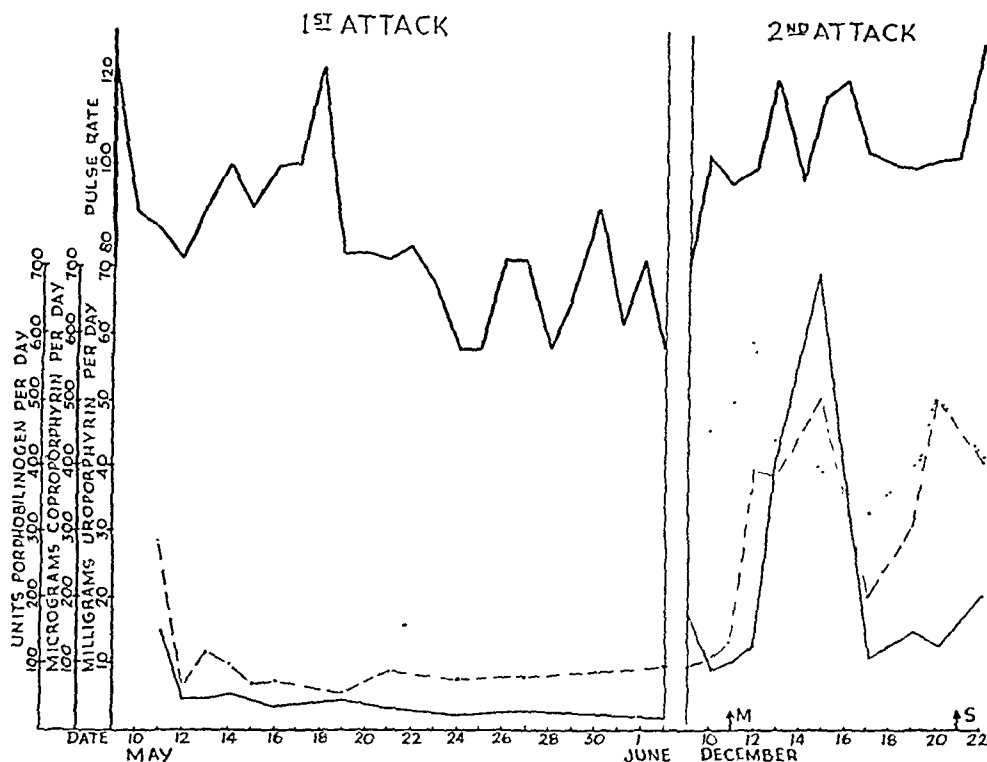
Fig. 4.—Coproporphyrin, uroporphyrin and porphobilinogen. (—.—. coproporphyrin micrograms per day; ——— uroporphyrin mg. per day; ...... porphobilinogen units per day; ——— midnight pulse rate; M,—methionine therapy commenced. S.—methionine therapy stopped).

TABE 2.—*Fecal Excretion of Porphyrin*

Date	Total, Gm.	Coproporphyrin by Ether Extraction, Micrograms per 100 Gm.	Additional Coproporphyrin by Absorption, Micrograms per 100 Gm.	Total Coproporphyrin, Micrograms per 100 Gm.	Uroporphyrin, Micrograms per 100 Gm.
5/22-5/24.............	225	38	...	....	....
5/25-5/27.............	271	7.7	...	....	....
5/28-5/30.............	267	25.5	...	....	....
5/31-6/1.............	110	23.7	...	....	....
12/11................	...	344	...	....	....
12/18................	...	87.5	...	....	....
Port mortem.......	...	470	860	1.33	2.82

THE ISOLATION AND IDENTIFICATION OF THE PORPHYRINS

Urine.—During the first attack a sample of the urine was examined by Professor Rimington, who found an easily isolated uroporphyrin, the melting point of the ester being 253 to 255 C. The coproporphyrin was present only in a small amount, and he managed to obtain with

difficulty both coproporphyrin III and coproporphyrin I methyl ester in the approximate ratio of 2:1. The melting point of the former was 178 C.

During the second attack I examined 1,500 cc. of dark port wine–colored urine. Spectroscopically the bulk of the porphyrin appeared to be present as the metal complex. The urine was acidified with 75 cc. of glacial acetic acid and extracted with 500 cc. of ether. Forty cubic centimeters of light liquid petrolatum was added to facilitate the breaking down of the emulsion. After prolonged standing the remaining emulsion was spun off, leaving a brownish residue at the bottom of the tubes. The aqueous material, still exhibiting a weak metal complex spectrum, was again extracted with 500 cc. of ether, and the ether extracts combined. The emulsion was again spun down and the residue was washed with ether. The former was combined with the first residue and the latter returned to the combined ether extracts.
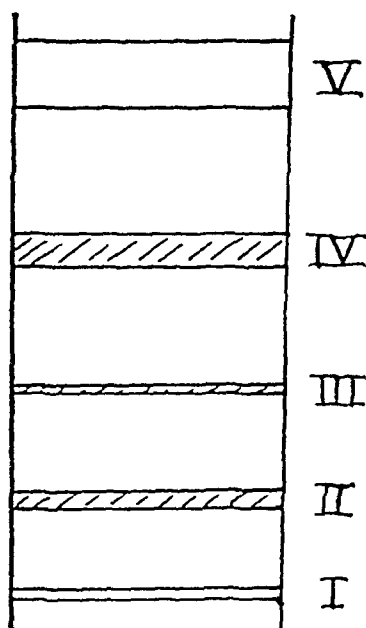
Fig. 5.—Composite diagram of the developed chromatogram of the liver extract. (Figures in brackets indicate ratio of chloroform and light liquid petrolatum in solvent required for elution. *I*, yellow pigment [1:10]; *II*, protoporphyrin [1:17]; *III*, porphyrin? [1:15]; *IV*, uroporphyrin [1:1]; *V*, greenish brown pigment.

Isolation of the Coproporphyrin: The combined ether extracts were prepared in the usual way, thrice washed with water and six times extracted with 1 per cent hydrochloric acid. At this stage no more porphyrin was extracted into the hydrochloric acid, but the ether still contained porphyrin. The ether was allowed to stand overnight over 1 per cent hydrochloric acid when all the porphyrin was finally extracted with five portions of 5 per cent hydrochloric acid.

After addition of sodium acetate to the combined hydrochloric extracts the porphyrin was transferred to ether, taken back to 0.25 per cent hydrochloric acid and thence back to ether. Most of the extraneous pigment had thus been removed. After removal of the ether the dry residue was esterified with methyl alcohol saturated with dry hydrochloric acid. The product crystallized from

chloroform–methyl alcohol was recrystallized four times from these solvents, being finally obtained as pale feathery crystals (fig. 6 *B*). The melting point [21] of the product was 236 to 241 C., indicating that it was mainly type I porphyrin.

Isolation of Waldenström's uroporphyrin: The precipitated residue from the ether extraction was first prepared. It was dissolved in 3 per cent solution of ammonia, and the precipitated phosphate was spun down. The spectrum of the ammonia solution exhibited four bands: 610, 570, 530 and 500 (extinction) millimicrons. The solution was acidified to p_H 4 with hydrochloric acid and allowed to stand overnight in the refrigerator. The precipitate was spun off, twice washed with 2 per cent acetic acid and dried over sulfuric acid. The residue was then treated with methyl alcohol and hydrochloric acid overnight and filtered on sintered glass from a small black residue. On admixture with chloroform and water a heavy black precipitate came down. This was separated by filtration and centrifugation and proved to be insoluble in hot chloroform, ammonia and 50 per cent hydrochloric acid. It was dissolved in 2 per cent acetic acid and exhibited a broad band from 505 to 495 millimicrons. Treated according to Schlesinger's technic it exhibited a dark green fluorescence. It was considered to be mainly porphobilin.

The chloroform solution was concentrated, and impure porphyrin ester crystals were obtained after the addition of methyl alcohol. One hundred and sixty milligrams of such material was obtained. This product was thrice recrystallized from chloroform and methyl alcohol, typical crystals of uroporphyrin III methyl ester being obtained (melting point 260 to 262 C.). The yield was 50 mg. Fractionation of the mother liquors yielded an additional 7 mg. of ester (melting point, 254 to 259 C.).

The Residual Porphyrin of the Aqueous Layer: The liquid residue after extraction with ether and separation of the solid deposit showed a weak spectrum of the metal complex. After preliminary experiments with other samples of urine, the following technic was adopted. The acid liquid was subjected to chromatography on a 20 cm. column of aluminum oxide. A light yellow band at the bottom of the column underwent elution while the last of the liquid was passing through the column. After adsorption was complete, the elution was begun with 750 cc. of 50 per cent (by volume) acetic acid. The first 400 cc. of eluate contained a strong solution of porphobilin giving a dark green fluorescence with Schlesinger's test. This eluate contained only traces of porphyrin. The passage of an additional 200 cc. of acetic acid brought out a considerable quantity of a mixture of free porphyrin and metal complex (spectrum 595, 578 and 540 millimicrons). Two hundred cubic centimeters of glacial acetic acid eluted a small quantity of metal complex. Finally elution with 150 cc. of 7 per cent ammonia brought out all the remaining pigment with most of the porphyrin.

This eluate was combined with the acetic acid eluate and brought to p_H 4. No porphyrin could be induced to precipitate during a fortnight. The liquid was therefore again passed through an aluminum oxide column at p_H 4, and the column was washed with 200 cc. of water, which eluted a small amount of porphyrin. The eluate was therefore adjusted to p_H 3.4 and again passed through the column, which was then washed with 250 cc. of water, no porphyrin then being removed. The porphyrin was completely eluted with 150 cc. of 10 per cent ammonia. The eluate was adjusted to p_H 4 with concentrated hydrochloric acid, when the porphyrin quantitatively precipitated out as pale brown

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21. This and all subsequent figures for melting points are corrected and determined by the micro method.
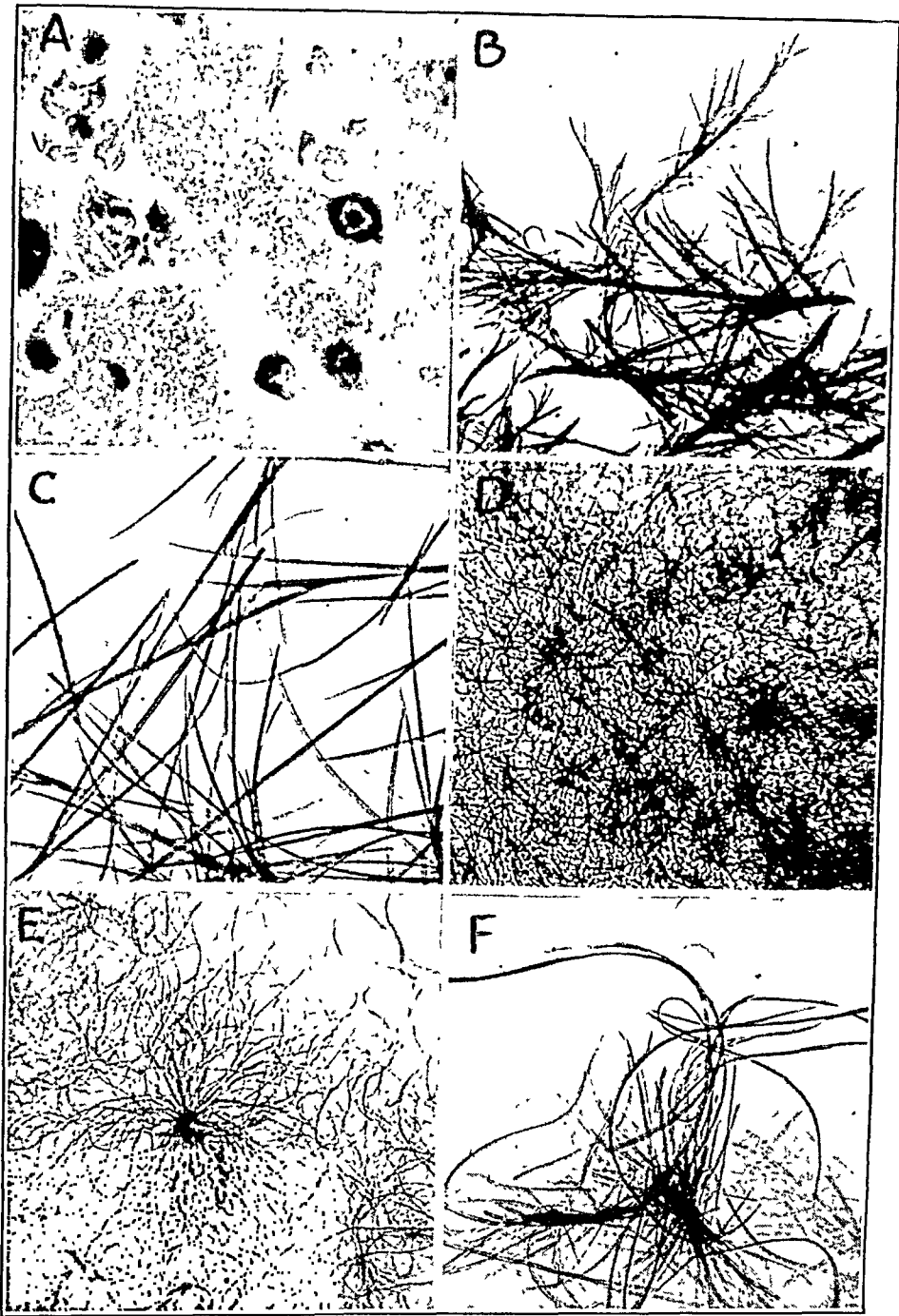
Fig. 6.—A, liver. Zone containing yellow and orange-red pigment granules (× 700); B, crystals of coproporphyrin I ester isolated from urine (the magnification in this and subsequent figures is × 350). C, crystals of coproporphyrin I ester isolated from feces; D, crystals of uroporphyrin I ester isolated from feces; E, crystals of uroporphyrin I ester isolated from liver; F, crystals of uroporphyrin

floccules. The precipitate was spun off, washed with 4 cc. of water, dried over sulfuric acid and esterified. After one recrystallization the melting point was 256 to 259 C. The yield was approximately 4 mg. A total yield of 61 mg. of Waldenström's uroporphyrin III methyl ester was therefore obtained from the 1,500 cc. sample of urine.

Feces.—Fifty grams of feces, obtained post mortem was partially dried and extracted by grinding with methyl alcohol and hydrochloric acid by the method of Schwartz and Watson[18] (1941). This process occupied two days. The
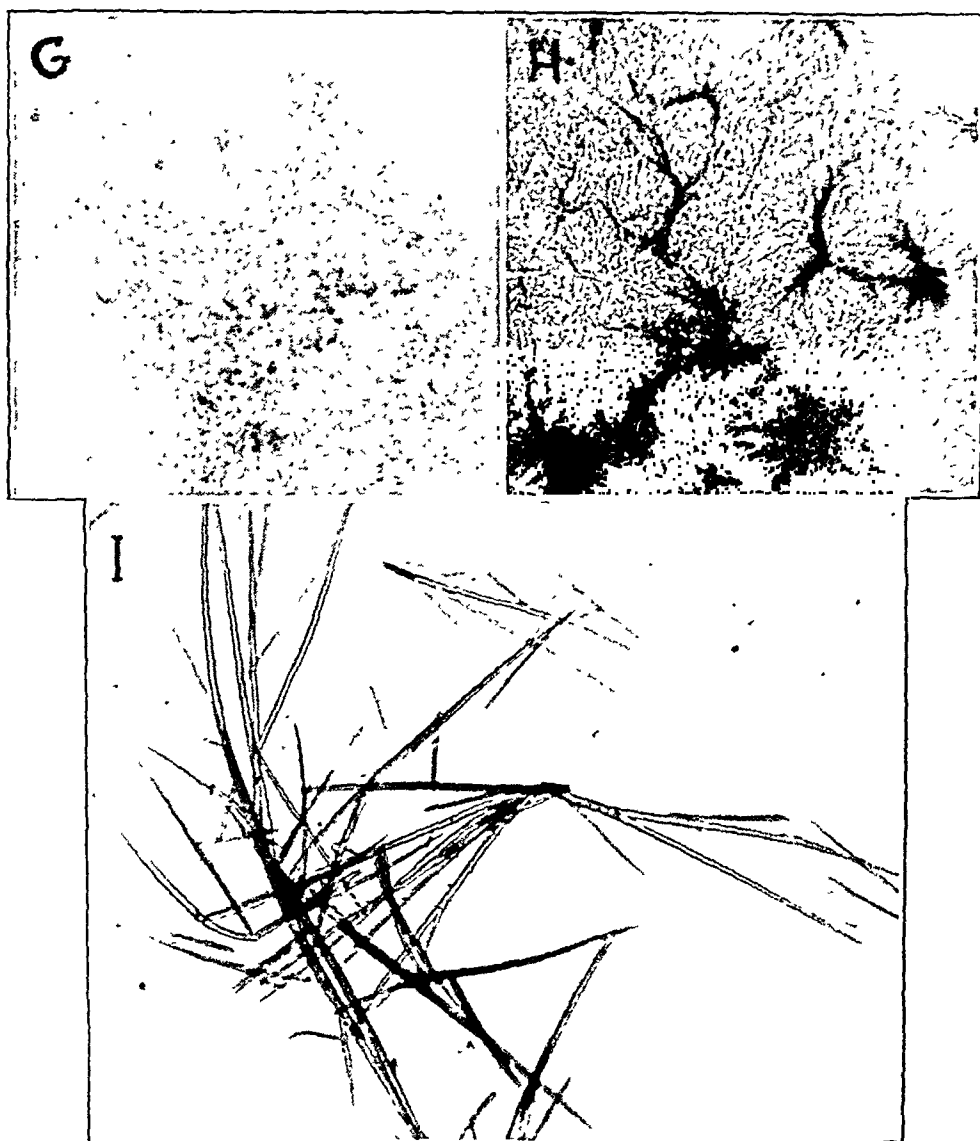
isolated from urine (after second esterification); *G*, material obtained from the "red-brown zone" on chromatography of the uroporphyrin isolated from the urine; *H*, the same material as that which is shown in *G*, after reesterification; *I*, crystals of coproporphyrin I ester obtained by decarboxylation of uroporphyrin isolated from urine.

esters were transferred to chloroform and washed with 7 per cent ammonia and 10 per cent sodium chloride, dried over anhydrous sodium sulfate and filtered. The volume of the chloroform was reduced to 48 cc. and 10 volumes of light liquid petrolatum added. After filtration of the precipitated material the

esters were adsorbed on an aluminum oxide column. The column was then treated with mixtures of chloroform and light liquid petrolatum of increasing chloroform content, each mixture first being used to extract the precipitate before passage through the column. Three zones of porphyrin developed.

Another chromatogram was made of zone I and gave but a single porphyrin band, which was eluted with chloroform and light liquid petrolatum (1:6). The solution contained a moderate quantity of protoporphyrin but was not further examined.

Zone II according to the second chromatogram developed two porphyrin bands. The lower band was eluted with chloroform and light liquid petrolatum (1:3.4) and on four recrystallizations yielded an unweighable quantity of coproporphyrin I methyl ester with a melting point of 250 to 252 C. (fig. 6 C). Crystals obtained from the mother liquor melted at 240 to 247 C. and were, therefore, mainly coproporphyrin I. The upper band, about equal in density in ultraviolet rays to that due to coproporphyrin, was eluted with chloroform and light liquid petrolatum (1:3), which also brought out some brownish pigment. This material could not be induced to crystallize. The bands in chloroform were 623, 582 to 564, 534 and 499 millimicrons.

Zone III was readsorbed on aluminum oxide from chloroform and light liquid petrolatum (1:6) and only a single porphyrin band could be developed. This was eluted with chloroform and light liquid petrolatum (1:1.4). Three crystallizations yielded 1.2 mg. of uroporphyrin ester with a melting point of 274 to 277 C. (fig. 6 D). Absorption bands in chloroform were 628, 588 to 565, 536 and 500 millimicrons.

Liver.—Fifteen grams of liver was extracted by the same technic as that used for the fecal extraction. No coproporphyrin could be identified with certainty in the ether extract, but a small amount of protoporphyrin was present. The residue from the ether extraction was extracted with methyl alcohol and hydrochloric acid and adsorbed on a column of aluminum oxide from chloroform and light liquid petrolatum (fig. 5). The 1:7 eluate contained traces of protoporphyrin, and 1:5 eluate brought out a further trace of porphyrin, which could not be identified. The 1:1 chloroform and light liquid petrolatum eluate removed an intense porphyrin band. The bands of the ester in chloroform were 627, 58 to 568, 535 and 501 millimicrons. An aliquot of the chloroform solution was used for fluorometric assay after saponification. This gave 0.61 mg. per hundred grams of wet weight tissue, i. e., 7 mg. in the entire liver.

Crystallization of the ester from the remainder of the chloroform solution yielded, after recrystallization, approximately 100 micrograms of uroporphyrin I ester, with a melting point of 282 to 285 C. (fig. 6 E).

Examination of Other Tissues for the Presence of Porphyrin.—The spleen, marrow and brain were analyzed by the same technic as that employed in the case of the liver. The only porphyrin identified was a trace of presumed protoporphyrin in each tissue.

Further Experiments on the Nature of the Uroporphyrin in the Urine.—Five milligrams of the uroporphyrin ester (melting point of 262 C.) was adsorbed onto precipitated calcium carbonate B. P. from benzene and light liquid petrolatum (3:1) (Grinstein, Schwartz and Watson,[7] 1945). Only two porphyrin bands developed. The lower was eluted with benzene and chloroform (5:1). On a second chromatogram it was an entity. The melting point of the ester was 260 to 261 C., and after reesterification and recrystallization it was 265 C. (fig. 6 F). The free porphyrin was soluble in ethyl acetate from aqueous solution at p_H 3.5.

The upper band was red-brown, as described by Grinstein, Schwartz and Watson [7] (1945), and could be eluted with chloroform only after addition of ⅙ volume of acetic acid. The eluate, after being washed with ammonia, yielded ill defined crystals with a melting point of 270 to 305 C. (fig. 6 *G*); the bands in chloroform (624, 570, 532 and 502 millimicrons [IV, III, II, I]) were not suggestive of the presence of much metal complex. Reesterification of this material gave a product with a melting point of 262 C. and of crystal form similar to that of material obtained from the lower band (fig. 6 *H*).

If the uroporphyrin ester, with a melting point of 262 C., isolated from the urine is reesterified before adsorption on calcium carbonate, adsorption on this material leads in the main to the development of a single band, only a minute amount of the "red-brown" zone at the top of the column being apparent.

Decarboxylations.—The uroporphyrin isolated from the urine (a melting point of 260 to 262 C.) and the reesterified material from the lower zone of the calcium carbonate chromatogram (a melting point of 265 C.) were subjected to decarboxylation. The ester was heated for three hours at 180 to 185 C. in 1 per cent hydrochloric acid. After cooling and the addition of sodium acetate the solution was extracted with ether and the ether washed with water to remove acetic acid and evaporated to dryness. The solid material was then esterified.

Uroporphyrin in the Urine.—Seven and five-tenths milligrams were decarboxylated, and the melting point obtained was 208 to 215 C. A chromatogram of this product was then made on calcium carbonate, being adsorbed from a mixture of equal parts of benzene and purified benzine (petroleum ether) and developed with benzene and chloroform (20:1). Three bands developed. At the top of the column was a small "red-brown" zone containing porphyrin. Next was a porphyrin band 1 cm. wide, immediately below which there was a distinct band 0.5 mm. in width, but this could not be separated from the main band and was eluted with it (*a*). The passage of chloroform through the column led to the development of a porphyrin band 1 mm. wide (*b*), which was eluted with chloroform. Crystallization of this product gave small rosettes of needles (melting point of 196 to 206 C.). Crystallization of the main product (*a*) yielded an ester with a melting point of 216 to 225 C. This was subjected to a second decarboxylation (as advocated by Grinstein, Schwartz and Watson [7] and Watson, Schwartz and Hawkinson [8] [1945]) and yielded an ester with a melting point of 215 to 225 and a yield of 3.4 mg. (44 per cent of starting material). The second decarboxylation had produced no appreciable change. Recrystallizing this product four times gave an ester with a melting point of 236 to 245 C., which was considered to be nearly pure coproporphyrin I methyl ester crystals (similar to fig. 6 *I*).

Chromatographed Uroporphyrin.—The whole of this material was decarboxylated. The melting point of the ester directly obtained was 207 to 215 C. After four recrystallizations nearly pure coproporphyrin I methyl ester was obtained (melting point, 238 to 245 C.) (fig. 6 *I*).

COMMENT

The clinical features of the case reported are classically those of acute idiopathic porphyria and require but little comment. From the therapeutic standpoint it is difficult to control the abdominal pain which is due to violent gastrointestinal spasm, severe contraction of

the stomach having been observed by Chandler, Harrison and Rimington [8] (1939). (See also Vannotti [10] [1937].) Fortunately, in the present case laparotomy was avoided. It is, however, remarkable how little effect antispasmodic drugs appear to have on this symptom. The mode of death in this patient was also classic, ascending paralysis being basically responsible.

The second case, discovered in the routine examination of the patient's relatives, was of the "latent type" of Waldenström. No history of symptoms ascribable to porphyria was noted, and there was no pathologic excretion of porphyrin. The familial incidence would be in agreement with Waldenström's [5] (1937) view that the condition is a dominant one, but it would appear from the present and the published data that the gene carries a low incidence of expression.

Quantitative studies of the excretion of porphyrin in acute porphyria are scanty, largely owing to the specialized methods required for their elucidation. Excretions of up to 50 mg. of uroporphyrin daily in the urine have been noted (measurements cited by Dobriner and Rhoads,[12] 1940). With the advent of a fairly rapid micro method devised by Rimington [17] (1943) it has now become possible to make such studies with frequent examinations of specimens. The only case in which this has so far been done appears to be that followed by Rimington himself, and the urinary excretion of uroporphyrin fluctuated wildly, even during the subsidence of symptoms. He also noted a general correlation between the pulse rate and the amount of porphyrin excreted. The present data are in general agreement with his observations but do not show such variation, with the exception of the peak in the excretion of coproporphyrin and uroporphyrin on December 15 (fig. 4). At this time there was some improvement in the abdominal pain, the maximum intensity having been reached two days previously. This in turn was preceded by twenty-four hours by a peak in the excretion of porphobilinogen, which, again, was preceded by the institution of methionine therapy. These facts are probably entirely fortuitous, but it is possible that they are in part significant. Consider first the relation to the excretion of porphobilinogen. Waldenström and Vahlquist [22] (1944) have placed great stress on the significance of the excretion of porphobilinogen in these cases. It may be accepted that its presence in the urine is of diagnostic value. However, they go as far as to postulate formation from porphobilinogen of the porphyrin excreted in the urine. Waldenström and Vahlquist [23] (1939) have demonstrated the formation of porphyrin from porphobilinogen in vitro, and this has been confirmed by me [24] (1945). There is now the

22. Waldenström, J., and Vahlquist, B.: Acta med. Scandinav. **117**:1, 1944.
23. Waldenström, J., and Vahlquist, B.: Ztschr. f. physiol. Chem. **260**:189, 1939.
24. Prunty, F. T. G.: Biochem. J., to be published.

fact to be considered that uroporphyrin has been demonstrated in the feces and with the aid of ultraviolet microscopy and chemical isolation, in the liver, thus confirming the observations of Watson (Grinstein, Schwartz and Watson,[7] 1945; Watson, Schwartz and Hawkinson,[8] 1945). Furthermore, porphobilinogen is present in the liver (Prunty,[24] 1945). But a study of figure 4 does not lend support to a close correlation between the excretions of porphobilinogen and of uroporphyrin. There is no quantitative evidence of increased excretion of porphobilinogen in vivo, but there is a close relation between this substance and the production of pigment (porphobilin) (Prunty,[24] 1945). It is clear, therefore, that further evidence is required before the role of porphobilinogen can be determined, especially in relation to its place as a precursor from which the pathologic porphyrin is derived.

The effect of methionine in the present case is open to doubt. It has often been suggested that in acute porphyria abnormal porphyrin metabolism may take place in the liver (Mason, Courville and Ziskind,[9] 1933; Turner,[13] 1940). In some of the cases reported in the literature, as in the present example, histologic changes of the necrotic type in the cells of the liver with abnormal amounts of brown or yellow iron-free pigment have been noted (Palmer,[25] 1939-1940; Correll, Peters and Murphy,[26] 1942; Nesbitt and Watkins,[27] 1942). In addition, there are a few cases in which biochemical evidence suggestive of hepatic damage has been obtained during life (Turner,[28] 1938; Nesbitt and Watkins,[27] 1942). Evidence of this type has also been forthcoming in the present study. Whether the hepatic changes are cause or effect is still open to doubt, but there are some who hold the latter to be the case (Mason, Courville and Ziskind,[9] 1933). It is also true that hepatic damage, such as hepatitis and cirrhosis, usually leads to a rise in the urinary-fecal ratio of excretion of coproporphyrin, in which the increase is usually type I porphyrin (Dobriner and Rhoads,[12] 1940; Nesbitt and Snell,[29] 1942). Excretion of uroporphyrin in such conditions has not been reported. The data in table 2 are too incomplete for one to draw any definite conclusions, especially in view of the fact that it was only later discovered that ether extraction of acidified feces yielded only a portion of the coproporphyrin content. The figures, however, do not suggest a rise in fecal coproporphyrin during remission. It also appears from figure 4 that methionine did

25. Palmer, H. W.: Ann. Int. Med. **13**:1500, 1940.

26. Correll, H. L.; Peters, B. J., and Murphy, F. D.: Urol. & Cutan. Rev. **46**:341, 1942.

27. Nesbitt, S., and Watkins, C. H.: Am. J. M. Sc. **203**:74, 1942.

28. Turner, W. J.: Studies on Porphyria, Arch. Int. Med. **61**:762 (May) 1938.

29. Nesbitt, S., and Snell, A. M.: Excretion of Coproporphyrin in Hepatic Disease, Arch. Int. Med. **69**:573 (April) 1942.

not have any beneficial effect, but rather if it had any effect it was in the reverse direction. It is possible that it might have stimulated the production of porphyrin from some such precursor as proline by a process of methyl donation, direct carboxylation now being recognized as a biologic process (Best and Lucas,[30] 1945; Krebs,[31] 1943).

Relation of the Porphyrin Isomer Excreted to the Type of Porphyria. —Waldenström[32] (1934) was the first to report the occurrence of uroporphyrin III in nature, considering it to be typical of acute porphyria. Since that time considerable stress has been put on the fact that the production and the excretion of uroporphyrin I are typical of congenital porphyria and of uroporphyrin III typical of the acute type. It seemed likely, therefore, that the type of the excretion of porphyrin might be related to the symptomatology of the condition, type III porphyrin having less photodynamic activity than type I. However, since Waldenström's work the excretion of type I uroporphyrin in acute porphyria has been found (Turner,[28] 1938; Grinstein, Schwartz and Watson,[7] 1945). The latter authors have also shown that type I uroporphyrin predominates, whereas the type of coproporphyrin appears more variable. Porphobilinogen, however, is a characteristic product only in the acute porphyria (Watson, Schwartz and Hawkinson,[8] 1945). In addition, a mixture of the symptomatology of acute and congenital porphyria is known to occur together (Nesbitt and Watkins,[27] 1942). My patient showed the usual absence of photosensitivity, even under provocation, and no large excess of porphyrin in the plasma or cerebrospinal fluid. The results of the biochemical studies show that the uroporphyrin isolated from the urine yielded an ester with a melting point of 265 C. for the best preparation, in fact yielded a high percentage of coproporphyrin I, the ester melting at 245 C. It seems not unusual to be unable to remove by fractional crystallization the last impurity, on occasion a melting point not above 245 C. being obtainable for coproporphyrin I methyl ester (Rimington,[4] 1936; Watson, Schwartz and Hawkinson,[8] 1945), whereas the accepted melting point for pure coproporphyrin I is 252 C. In addition, the uroporphyrin urine contained porphyrin other than uroporphyrin I. The material could not be separated into uroporphyrin I and a type III porphyrin, found by Watson, Schwartz and Hawkinson[8] (1945) by absorption onto calcium carbonate and it therefore appeared to be a "Waldenström type B porphyrin," as classified by Watson. Decarboxylation either of the material isolated from the urine or of a specimen

30. Best, C. H., and Lucas, C. C., in Harris, R. S. and Thimann K. V.: Vitamins and Hormones, New York, Academic Press, Inc., 1943, vol. 1, p. 1.

31. Krebs, H. A., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1943, vol. 12, p. 529.

32. Waldenström, J.: Acta med. Scandinav. 83:281, 1934.

separated by chromatography from the "red-brown" impurity yielded finally the same product, mainly nearly pure coproporphyrin I. There was clear evidence of the presence of other porphyrins, but neither could type III porphyrin be isolated nor could the product of decarboxylation with a melting point of 219 to 226 C. be identified. Chromatography of the product from the first decarboxylation yielded a small amount of porphyrin, the melting point of the ester being 196 to 206 C. This may be a less pure form of Watson's heptamethyl ester with a melting point of 224 C. from which he obtained coproporphyrin I by further decarboxylation. The melting points of the esters of the small amounts of the uroporphyrin isolated from the liver and the feces (282 to 285 C. and 274 to 277 C. respectively) indicate that they were nearly pure uroporphyrin I octamethyl esters.

The coproporphyrin isolated from the urine and the feces was predominantly type I porphyrin, the feces yielding the purer specimen.

SUMMARY

Two cases of porphyria are recorded, one being the "latent type" of Waldenström. The other case exhibited the typical symptoms and course of acute porphyria.

Evidence of mild hepatic impairment was obtained. Histologic evidence of necrosis was found with deposits of brownish yellow granules in the cells of the liver in areas found by ultraviolet microscopic examination to contain porphyrin. The importance of the liver in the pathogenesis of the disease has been discussed.

Measurements of the excretion of coproporphyrin and uroporphyrin in the urine and the feces during two attacks are recorded. In addition, the excretion of porphobilinogen in the urine in one attack has been determined and its importance in relation to the formation of porphyrin examined.

A uroporphyrin described by Waldenström as type III has been isolated from the urine. This has been shown on further examination to be largely type I porphyrin.

Uroporphyrin I has also been obtained from the liver and the feces. Coproporphyrin I has been isolated from the urine and the feces.

Ultraviolet microscopic examination showed the presence of moderate amounts of porphyrin in the kidneys, especially the renal tubules, and in the costal cartilage. The emission spectrum suggested the latter may contain protoporphyrin.

The importance of the fact that type I porphyrins are found in both acute and congenital porphyrias has been indicated, and the added dif-

ficulties of explaining the differing symptomatology of these conditions have ben discussed.

PERIPHERAL BLOOD FLOW, RECTAL AND SKIN TEMPERATURE IN CONGESTIVE HEART FAILURE

The Effects of Rapid Digitalization in This State

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CLINICIANS have been under the impression that the skin of patients with congestive heart failure, especially the skin of the extremities, seemed cooler than normal even at a time when fever was present. Steele and Cohn [1] have made objective measurements relating to the temperature of the skin of certain areas of the body and to the rectal temperature in patients with heart failure in an attempt to arrive at an understanding of the fever which occurs in heart failure unrelated to any infection. They found that the "temperature of the surface in cardiac patients is lower than in normal individuals, while that of patients with infectious fever is as high as or higher than normal. The difference in behavior leads to the conclusion that the elevation of rectal temperature in heart failure depends on processes incidental to heart failure itself." [1a] Certain things are known about the circulation in heart failure and the effects of digitalis in this state. Stewart and Cohn,[2] Stewart, Deitrick, Crane and Wheeler,[3] Stewart, Crane, Watson,

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1. (a) Steele, J. M.: Fever in Heart Failure; Relations Between the Temperatures of the Interior and the Surface of the Body, J. Clin. Investigation **13**:869, 1934. (b) Cohn, A. E., and Steele, J. M.: Unexplained Fever in Heart Failure, ibid. **13**:853, 1934. (c) Steele, J. M.: Fever in Heart Disease, Internat. Clin. **1**:17, 1936.

2. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: III. Part I. The Effect on the Output in Normal Human Hearts; Part II. The Effect on the Output of Hearts in Heart Failure with Congestion, in Human Beings, J. Clin. Investigation **11**:917, 1932.

3. Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Wheeler, C. H.: Action of Digitalis in Uncompensated Heart Disease, Arch. Int. Med. **62**:569 (Oct.) 1938.

Wheeler and Deitrick[4] and McGuire, Hauenstein and Shore[5] have shown that the cardiac output per minute and per beat of the heart is low in the presence of congestive heart failure and that the heart is dilated at a time when the velocity of blood flow is slow and the venous pressure elevated.[6] The exhibition of digitalis under those circumstances decreased the size of the heart and increased the volume output of blood from the heart per minute and per beat, resulting in an increase in velocity of blood flow and a fall in venous pressure.[6] Abramson, Fierst and Flachs,[7] using the method of venous occlusion in taking plethysmographic readings, found in patients with chronic congestive heart failure that the blood flow to edematous limbs was within the range of that observed in normal subjects. Certain experimental data pointed to a decrease in the amount of blood allotted to the peripheral blood flow in congestive heart failure, while others indicated a normal blood flow in the extremities. Objective measurements with respect to the total peripheral blood flow have not been available to clarify this question. To supply this information was the object of the observations now being reported.

<div align="center">MATERIAL</div>

Studies were made of 15 patients suffering from heart failure before and after the exhibition of digitalis bodies. The drug was given intravenously in order that there might be a comparison of the peripheral blood flow immediately before injection with the flow at intervals immediately, as well as at longer intervals, afterward.

Strophanthin K was chosen[8] because its effects are detectable a matter of minutes after injection. Patients exhibiting auricular fibrillation as well as those with normal sinus mechanism were available for study, and those in the various etiologic categories of heart disease— namely, rheumatic, arteriosclerotic and hypertensive—were represented.

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4. Stewart, H. J.; Crane, N. F.; Watson, R. F.; Wheeler, C. H., and Deitrick, J. E.: The Cardiac Output in Congestive Heart Failure and in Organic Heart Disease, Ann. Int. Med. **13**:2323, 1940.

5. McGuire, J.; Hauenstein, V., and Shore, R.: Cardiac Output in Heart Disease Determined by the Direct Fick Method, Including Comparative Determinations by the Acetylene Method, Arch. Int. Med. **60**:1034 (Dec.) 1937.

6. Stewart and Cohn.[2] Stewart, Deitrick, Crane and Wheeler.[3] Stewart and others.[4]

7. Abramson, D. I.; Fierst, S. M., and Flachs, K.: Rate of Peripheral Blood Flow in the Presence of Edema, Am. Heart J. **25**:328, 1943.

8. (a) Brams, W. A.; Golden, J. S.; Sanders, A., and Kaplan, L. G.: Observations on Toxicity and Clinical Value of Strophanthin, Ann. Int. Med. **13**:618, (Oct.) 1939. (b) Eichna, L. W., and Taube, H.: A Comparison of the Action of Four Cardiac Glycosides on a Patient with Congestive Heart Failure, Am. Heart J. **26**:631, 1943; (c) The Effect of Intravenously Administered Digoxin and Ouabain on the Systemic Venous Pressure of Patients with Congestive Heart Failure, ibid. **27**:641, 1944.

In addition to strophanthin K, which is known to exhibit its effects shortly after injection, digitaline Nativelle, which can also be given intravenously, was used. This drug was chosen because it induces its effects more slowly.[8b] Nine patients were given strophanthin K; 2 of these patients received the drug on two occasions. Digitaline Nativelle was given to 8 patients.

PLAN OF OBSERVATIONS

All patients were admitted to the hospital and placed at complete rest in bed. The intake of fluid was usually limited to 1,200 cc. per day, and the intake of salt to 3 Gm. Before the drug was given, four sets of observations of rectal and skin temperatures were made from which three control levels of peripheral blood flow could be estimated. Blood pressure and heart rate were recorded between the other observations. Single basal metabolic rate, circulation time, venous pressure and electrocardiogram served as controls. Electrocardiograms were afterward made at intervals of ten to thirty minutes for all patients, except L. B., who were receiving strophanthin K; for only 2 patients given digitaline Nativelle (M.H. and E.P.) were electrocardiograms taken. After control observations were made, the drug selected for studying was given intravenously. Beginning fifteen minutes after the injection, all the observations were repeated at twenty minute intervals for seventy to one hundred and eighty minutes afterward, the average length of time being ninety-five minutes. In some instances measurements were made twenty-four to forty-eight hours later, as well as at longer intervals. All of the data on a patient secured before injection were averaged to give an estimate of the peripheral blood flow and other conditions prevailing before the injection of digitalis. All of the measurements taken after the injection for the morning were averaged and are recorded in the table; the maximum single peripheral blood flow recorded after injection is also shown. One or two basal metabolic rates were recorded after the injection of the digitalis preparation, for integration in the calculation of the peripheral blood flow. The longest continuous observations relating to the effects of the drug covered one hundred and eighty minutes. Observations were not continued beyond this time because patients might become restless and not be considered basal. For 1 patient given digitaline Nativelle, however, observations were started three hundred minutes after the injection and continued for one hour.

All observations were made in the morning with the patients in a basal metabolic state. Patients were brought to the constant temperature room on a stretcher and lay in bed, arms at sides, covered only with a sheet, for one hour in order to become adjusted to the room temperature of 25 C. and the humidity of 45 to 50 per cent.

Observations on Pat

Name, Sex, Age (Yr.)	Date	Amount of Drug Intravenously, Mg.	Time with Reference to Drug	Peripheral Blood Flow, Cc./M²/Min.	Maximum Peripheral Blood Flow; Min. After Drug, Cc./M²/Min.	Rectal Temperature, °C	Average Skin Temperature, °C	Temperature (Centigrad				
								1	2	3	4	5
. N. F 58	3/18/41 3/18/41 4/ 7/41	.... 0.25	Before 78 min. after 28 days after	97 116 110	.... 131 cc. 78 min.	37.22 37.46 37.50	34.09 34.12 33.86	34.2 35.1 34.8	34.5 35.7 35.1	36.2 36.7 35.6	35.6 35.1 34.2	34.3 34.2 34.3
. R. M 41	1/16/40 1/16/40 1/17/40 1/17/40 1/25/40 2/ 3/40	...: 0.125 .... 0.125	Before 137 min. after Before 131 min. after 8 days after 17 days after	5 14 16 24 57 23	.... 17 cc. 84 min. .... 27 cc. 56 min.	37.63 37.59 37.14 37.05 36.99 37.20	31.71 31.91 32.66 32 45 33.79 32.63	30.9 31.2 30.7 30.8 33.9 33.5	32.3 33.2 33.7 32.7 34.4 34.3	33.5 34.0 34.4 34.5 34.4 33.9	34.2 34.3 34.1 34.4 34.6 34.2	31.9 32.3 32.9 32.3 33.7 32.8
. P. M 68	4/ 7/42 4/ 7/42	.... 0.25	Before 80 min. after	31 41	.... 61 cc. 40 min.	36.99 36.92	33.30 33.01	34.0 34.1	34.1 34.4	33.9 33.9	34.3 34.3	33.2 32.4
). S. F 41	4/ 8/42 4/ 8/42 4/11/42	.... 0.25	Before 65 min. after 3 days after	36 52 43	.... 74 cc. 65 min.	37.29 37.26 36.82	32.96 33.12 32.93	34.5 34.5 34.2	34.6 34.9 34.0	34.7 34.7 33.8	33.9 33.9 33.4	32.5 32.6 31.1
'. R. M 38	9/16/41 9/16/41 9/17/41 9/17/41 10/ 6/41	.... 0.25 .... 0.25	Before 60 min. after Before 67 min. after 19 days after	14 38 14 36 13	.... 70 cc. 60 min. .... 58 cc. 67 min.	37.89 37.94 37.69 37.78 37.39	32.48 33.14 32.57 32.71 33.10	32.9 33.9 32.6 33.4 33.7	33.2 34.1 33.1 32.5 34.1	33.2 33.3 33.3 33.5 33.5	33.8 34.5 33.6 33.7 33.8	33.1 33.7 32.9 33.4 33.6
I. H. M 51	1/10/42 1/19/42 1/19/42	.... 0.25	Before Before 70 min. after	21 4 27	.... 40 cc. 70 min.	37.54 37.43 37.52	33.80 33.09 33.67	34.5 34.0 34.6	35.6 34.9 35.4	34.9 34.4 35.1	35.4 34.6 35.3	33.7 33.4 33.8
I. W. M 63	2/16/42 2/16/42 2/28/42	.... 0.25	Before 73 min. after 12 days after	46 90 83	.... 99 cc. 73 min.	37.38 37.37 37.26	33.58 33.61 34.12	34.0 33.5 34.3	34.7 34.7 34.8	34.6 35.0 34.9	34.3 35.1 35.2	33.9 34.1 34.2
L. B. F 20	7/14/42 7/14/42 7/20/42 7/21/42	.... 0.125	Before 180 min. after 6 days after 7 days after	31 84 22 28	.... 148 cc. 50 min.	37.68 37.61 37.96 36.18	33.23 32.93 32.02 32.22	34.0 33.4 32.2 32.9	35.0 34.5 33.5 33.8	34.9 34.7 33.9 34.3	35.2 34.7 33.3 33.6	33.6 33.4 31.9 32.2
. B. F 38	5/23/44 5/23/44 5/25/44	.... 0.125	Before 130 min. after 2 days after	27 33 20	.... { 60 cc. 30 min. } { 60 cc. 70 min. }	38.29 38.38 38.16	32.75 32.77 31.90	34.5 34.7 33.6	35.3 35.1 33.1	35.1 35.1 33.8	33.1 33.3 32.2	32.6 32.9 30.3
verage Before..........................				29	....	37.56	32.95	33.3	34.0	34.4	34.2	33.1
verage After...........................				50	71 cc. 64 min.	37.53	33.07	33.6	34.4	34.6	34.4	33.2

Observations on Pati

'. L. M 54	5/26/43 5/26/43 5/27/43 5/29/43 6/ 3/43	.... 1.2	Before 110 min. after 24 hrs. after 3 days after 7 days after	33 53 16 13 29	.... 88 cc. 110 min.	37.11 37.12 37.04 37.11 37.58	33.48 33.37 33.47 33.14 33.41	35.0 34.9 34.4 34.4 34.4	34.8 35.1 34.6 34.3 34.6	34.6 34.8 34.2 33.9 34.1	35.0 34.9 34.5 34.2 34.3	33.9 33.9 33.7 33.0 33.5
.O'S. M 39	6/ 9/43 6/ 9/43 6/10/43	.... 1.2	Before 112 min. after 24 hrs. after	60 51 27	.... 49 cc. 92 min.	37.48 37.60 37.72	33.40 33.36 33.23	34.6 34.5 34.9	34.3 34.1 34.5	34.2 34.1 34.4	34.5 34.6 34.6	33.3 32.9 33.2
. K. F 55	3/15/44 3/15/44 3/23/44 4/ 8/44 4/10/44	.... 1.2	Before 90 min. after 8 days after 24 days after 26 days after	25 25 33 56 33	.... 44 cc. 73 min.	37.55 37.64 37.07 37.08 37.11	31.74 31.66 32.13 32.58 32.00	32.0 32.2 33.1 34.2 33.4	33.4 33.3 33.6 34.2 33.6	32.2 32.2 33.4 33.8 33.4	31.7 31.6 31.9 31.7 31.4	31.1 30.9 31.8 32.7 32.2
. H. F 75	3/28/44 3/28/44 3/30/44	.... 1.2	Before 133 min. after 2 days after	51 42 54	.... 63 cc. 53 min.	37.29 37.52 37.35	33.20 33.33 33.29	34.3 34.4 34.0	34.4 34.4 34.8	34.2 34.6 34.5	32.8 33.3 33.5	33.5 34.0 33.3
I. M. F 60	3/18/44 3/18/44	.... 1.2	Before 90 min. after	59 51	.... 70 cc. 90 min.	37.82 37.93	33.66 33.52	33.5 33.7	35.3 35.1	35.3 35.1	34.7 34.6	33.6 33.4

Given Strophanthin K

Eleven Areas on Body Surface					Heart Rate,* per Min.	Pulse Rate per Min.	Blood Pressure, Mm. Hg.	Basal Metabolic Rate, per Cent	Circulation Time, Sec.	Venous Pressure, Mm. Saline	Diagnosis
7	8	9	10	11							
33.9	34.0	33.5	32.6	30.9	83	90	170/112	+36	25	133	Hypertensive and arteriosclerotic heart
33.9	34.2	33.0	32.5	30.2	87	84	183/113	+36	22	132	disease; enlarged heart; auricular fibrilla-
34.1	32.9	32.8	32.9	30.7	73	68	188/97	+28	18	84	tion; congestive heart failure.
28.4	33.2	31.8	30.8	26.5	150	76	....	+25	52	246	Rheumatic heart disease; mitral stenosis
27.1	33.7	32.1	31.0	27.0	156	..	....	+23	68	248	and insufficiency; functional tricuspid
32.9	33.1	31.3	30.3	30.3	130	80	....	+13	68	280	insufficiency; enlarged heart; auricular
32.0	33.5	31.3	31.2	28.9	136	101	....	+22	40	218	fibrillation; congestive heart failure.
34.6	33.5	32.7	32.7	34.0	89	88	135/88	+ 6	46	242	
33.5	32.3	31.3	29.8	31.8	72	69	119/65	+ 5	31	62	
34.3	32.7	32.0	32.1	32.9	59	60	170/97	+10	35	70	Hypertensive and arteriosclerotic heart
33.5	32.4	31.6	31.4	32.1	65	61	165/95	+ 7	35	75	disease; enlarged heart; normal rhythm;
											congestive heart failure.
34.2	31.5	30.7	31.3	32.8	91	97	170/127	+ 6	22	80	Hypertensive heart disease; enlarged heart;
33.7	31.6	30.7	31.8	33.6	83	84	163/124	− 9	17	68	normal rhythm; congestive heart failure.
34.0	31.7	31.6	32.6	33.2	86	72	169/110	− 7	13	100	
33.2	31.5	30.9	31.0	32.6	115	116	180/145	+25	..	...	Hypertensive heart disease; enlarged heart;
33.8	31.7	31.4	31.2	33.7	112	111	180/140	+35	24	233	normal rhythm; congestive heart failure.
33.2	31.8	31.6	31.1	33.1	100	105	168/138	+13	20	210	
33.3	31.8	31.5	31.1	33.0	108	107	163/141	+24	20	209	
33.4	32.5	31.9	31.9	32.6	75	79	171/123	+ 1	13	67	
34.3	33.1	31.7	32.2	32.9	95	105	100/80	+ 7	46	243	Hypertensive heart disease; enlarged heart;
34.0	32.6	31.6	31.2	29.7	94	103	102/80	+ 3	56	242	angina; normal rhythm; congestive
34.4	33.0	31.8	31.7	31.7	86	91	104/82	+ 3	44	165	heart failure.
34.3	32.7	31.4	32.9	33.2	77	80	146/85	+35	23	84	Pulmonary heart disease; cor pulmonale;
34.1	32.5	31.2	32.7	33.0	80	77	141/79	+44	20	80	pulmonary fibrosis and emphysema;
34.5	32.8	33.2	32.4	33.6	..	71	156/89	+19	16	62	chronic bronchitis; enlarged heart;
											normal rhythm; congestive heart failure.
32.7	34.0	31.5	30.7	30.4	120	92	113/71	+33	28	119	Rheumatic heart disease; mitral stenosis
32.5	33.6	31.3	30.4	29.9	118	79	112/72	+29	25	72	and insufficiency; enlarged heart; auricu-
32.3	32.5	29.7	30.0	30.7	78	65	133/94	+ 8	..	...	lar fibrillation; congestive heart failure.
32.9	31.8	29.2	30.0	30.4	72	62	135/95	+ 6	33	64	
34.1	30.9	31.3	30.7	30.2	124	78	92/64	+32	..	...	Rheumatic heart disease; mitral stenosis
33.7	31.1	31.7	30.7	29.9	106	65	102/60	+30	..	...	and insufficiency; enlarged heart; auricu-
34.6	29.6	29.5	30.0	33.6	146	79	107/61	+24	..	...	lar fibrillation; congestive heart failure.
33.2	32.5	31.6	31.4	31.1	104	89	119/84	+21	37	163	
32.9	32.6	31.6	31.5	31.2	104	76	119/82	+22	33	158	

Given Digitaline Nativelle

34.7	33.8	30.9	31.2	31.2	90†	84	108/77	+25	..	...	Rheumatic and arteriosclerotic heart
34.2	33.3	30.5	31.0	30.2	..	73	112/77	+31	..	...	disease; mitral stenosis and insufficiency;
34.2	33.6	31.5	31.6	32.6	..	59	112/74	+24	..	...	enlarged heart; auricular fibrillation;
34.3	32.7	31.1	31.7	31.7	75	60	107/72	+11	..	...	congestive heart failure.
34.6	33.2	31.1	31.8	32.9	..	62	111/71	+19	..	...	
34.3	33.5	32.5	31.9	30.8	100	90	94/66	+22	..	...	Rheumatic heart disease; mitral stenosis
34.4	33.0	32.1	32.0	31.9	96	79	96/66	+22	..	...	and insufficiency; auricular fibrillation;
34.5	33.3	31.4	31.8	28.6	..	78	96/60	+17	..	...	no signs of heart failure.
33.6	30.9	30.5	30.7	31.4	124	118	164/92	+49	..	...	Hypertensive and arteriosclerotic heart
33.3	30.6	30.2	30.9	31.7	113	101	174/107	+56	..	...	disease; enlarged heart; auricular
33.4	31.2	30.8	31.2	30.6	76	73	128/83	+23	..	...	fibrillation; heart failure.
33.9	31.4	31.1	31.5	32.2	86	79	123/79	+36	..	...	
33.2	30.9	30.7	31.0	30.9	78	70	133/78	+37	..	...	
34.9	31.8	31.7	31.8	33.9	85	84	142/67	+28	..	...	Hypertensive and arteriosclerotic heart
34.8	31.9	31.3	31.8	34.1	83	82	164/65	+33	..	...	disease; enlarged heart; auricular
35.0	32.0	31.4	31.8	34.1	74	74	154/67	+31	..	...	fibrillation; no signs of heart failure.
33.7	33.5	33.2	32.3	30.7	101	94	123/72	+31	..	...	Arteriosclerotic heart disease; enlarged
34.1	32.7	32.6	32.3	31.0	85	83	144/68	+31	..	...	heart; auricular fibrillation; congestive
											heart failure.

Name, Sex, Age (Yr.)	Date	Amount of Drug Intravenously, Mg.	Time with Reference to Drug	Peripheral Blood Flow, Cc./M²/Min.	Maximum Peripheral Blood Flow; Min. After Drug, Cc./M²/Min.	Rectal Temperature, °C	Average Skin Temperature, °C	Temperature (Centigrade) of					
								1	2	3	4	5	6
W. M.	4/ 1/44	....	Before	35	....	37.23	33.60	35.0	34.8	34.2	35.0	33.4	33.1
M	4/ 1/44	1.2	132 min. after	36	70 cc. 112 min.	37.16	33.55	34.7	35.4	34.4	33.5	34.0	33.2
45	4/ 3/44	....	2 days after	21	....	37.85	33.06	34.8	34.3	34.1	34.6	32.9	32.4
M. H.	1/22/42	....	Before	12	....	37.22	33.23	34.0	34.6	34.4	34.8	33.2	33.2
M	1/22/42	1.2	5 hrs. after	93	97 cc. 5 hrs.	37.20	34.50	35.1	35.5	35.8	35.7	33.8	33.3
51													
E. P.	4/10/42	....	Before	19	....	37.00	33.02	34.3	34.1	33.5	33.8	32.7	32.5
M	4/10/42	1.2	70 min. after	25	36 cc. 80 min.	37.00	33.71	34.2	34.9	33.2	33.7	32.4	32.3
68	4/10/42	....	150 min. after	36	....	36.85	32.95	34.3	33.9	33.4	33.9	32.9	32.9
Average Before........................				37	....	37.34	33.17	34.1	34.6	34.2	34.0	33.1	33.2
Average After........................				48	65 cc. 114 min.	37.40	33.20	34.2	34.7	34.3	34.0	33.2	33.2
Average of all patients before digitalis bodies	19 measurements on 15 patients			32	....	37.44	33.03	33.6	34.2	34.3	34.2	33.1	32.8
Average of all patients after digitalis bodies	19 measurements on 15 patients			49	....	37.50	33.19	33.9	34.5	34.4	34.3	33.2	32.8
Normal subjects at 25 C.[20]	25 measurements on 24 patients			33	....	36.72	32.82	33.92	33.66	33.44	33.59	32.67	32.45

* These rates were calculated from electrocardiograms and were not synchronous with the pulse rates, which
† Electrocardiograms were not taken during these observations except in the case of E. P., and the rates in this

The blood pressure cuff placed on the patient's left arm and electrodes for deriving the electrocardiograms remained in place throughout the morning.

Of strophanthin K.[9] 0.25 mg. was given intravenously to all patients except those with mitral stenosis, to whom half of this amount, namely, 0.125 mg., was administered. Of digitaline Nativelle 1.2 mg. was given intravenously. The injections were given slowly, five to ten minutes being required for injection. The following patients given strophanthin K had normal rhythm: M.H., E.P., D.S., F.R. and M.W.; the following had auricular fibrillation: L.B., V.B., E.N. and J.R. Of those patients given digitaline Nativelle, M.H. and E.P. had normal rhythm and F.L., M.O'S., N.K., K.H., M.M. and W.M. had auricular fibrillation.

METHODS

The peripheral blood flow was measured by our modification[10] of the method of Hardy and Soderstrom.[11] In this method the average peripheral blood flow for the whole body is estimated as cubic centimeters per square meter of the body surface per minute, rather than the

9. The Abbott Laboratories supplied the strophanthin K used in these studies.

10. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, Am. Heart J. **20**:205, 1940. Stewart, H. J., and Evans, W. F.: Peripheral Blood Flow in Myxedema, Arch. Int. Med. **69**:808 (May) 1942.

11. Hardy, J. D., and Soderstrom, G. F.: Heat Loss from the Nude Body and Peripheral Blood Flow at Temperatures of 22° C. to 35° C., J. Nutrition **16**:493, 1938.

Eleven Areas on Body Surface					Heart Rate,* per Min.	Pulse Rate per Min.	Blood Pressure, Mm. Hg.	Basal Metabolic Rate, per Cent	Circulation Time, Sec.	Venous Pressure, Mm. Saline	Diagnosis
7	8	9	10	11							
35.0	32.7	32.1	31.4	33.7	92	83	104/78	+ 3	..	..	Postoperative chronic constrictive pericarditis; enlarged heart; auricular fibrillation; heart failure.
34.6	32.6	31.9	30.9	33.5	90	84	112/71	+ 3	..	...	
34.1	32.5	31.7	31.3	31.4	72	70	97/67	+ 2	..	..	
33.2	33.8	33.0	31.6	30.0	..	97	117/82	+ 5	49	184	Hypertensive heart disease; enlarged heart; angina; normal rhythm; congestive heart failure.
34.5	34.0	33.6	33.0	34.3	..	100	126/86	+ 8	51	161	
34.5	32.7	31.1	31.4	32.0	68	68	175/113	+ 6	33	112	Hypertensive and arteriosclerotic heart disease; enlarged heart; normal rhythm; congestive heart failure.
34.7	31.7	31.0	31.0	32.6	68	68	173/104	+13	32	112	
34.5	32.4	31.2	31.0	32.0	..	68	178/113	....	33	100	
34.2	32.8	31.9	31.5	31.7	94	90	128/81	+21	..	...	
34.3	32.5	31.7	31.6	32.4	87	73	138/81	+25	..	...	
33.6	32.7	31.7	31.5	31.4	95	89	123/82	+21	..	...	
33.5	32.6	31.5	31.5	31.7	93	70	127/82	+23	..	...	
33.59	32.39	32.11	32.22	30.91	..	..	....	− 3	..	...	

accounts for discrepancies in rates.
column are apical heart rates.

blood flow prevailing in local areas. Measurements were made at twenty minute intervals except in the case of V.B., for whom they were made at ten minute intervals, and in that of J.R., for whom the intervals varied.[12] For the estimation of peripheral blood flow by this method recordings were made (*a*) of the temperature of the skin from 11 areas on the surface of the body (fig. 1), by means of the Hardy radiometer [13]; (*b*) of the rectal temperature by means of a copper-constantan thermocouple [11]; (*c*) of the basal metabolic rate with a Benedict-Roth apparatus.[14] The tables of Du Bois and Du Bois [15] were used in estimating the surface area, and of the Mayo Clinic [16] in calculating the basal metabolic rate.

The circulation time was measured with dehydrocholic acid [17] and the venous pressure by the direct method of Taylor, Thomas and

12. In the calculations the formulas allow for such variations.

13. Hardy, J. D., and Soderstrom, G. F.: An Improved Apparatus for Measuring Surface and Body Temperature, Rev. Scient. Instruments **8**:419, 1937.

14. Roth, P.: Modifications of Apparatus and Improved Technique Adaptable to the Benedict Type of Respiration Apparatus, Boston M. & S. J. **186**:457, 1922.

15. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. **17**:863 (June) 1916.

16. Boothby, W. M.; Berkson, J., and Dunn, H. J.. Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism, with a Nomogram for Clinical Application, Am. J. Physiol. **116**:468, 1936.

17. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1933.

Schleiter.[18] Both these measurements were made in free intervals, with only one venipuncture and without a tourniquet, at such a time that basal conditions were restored by the time the interval had arrived for recording the skin and rectal temperatures. This precaution was taken
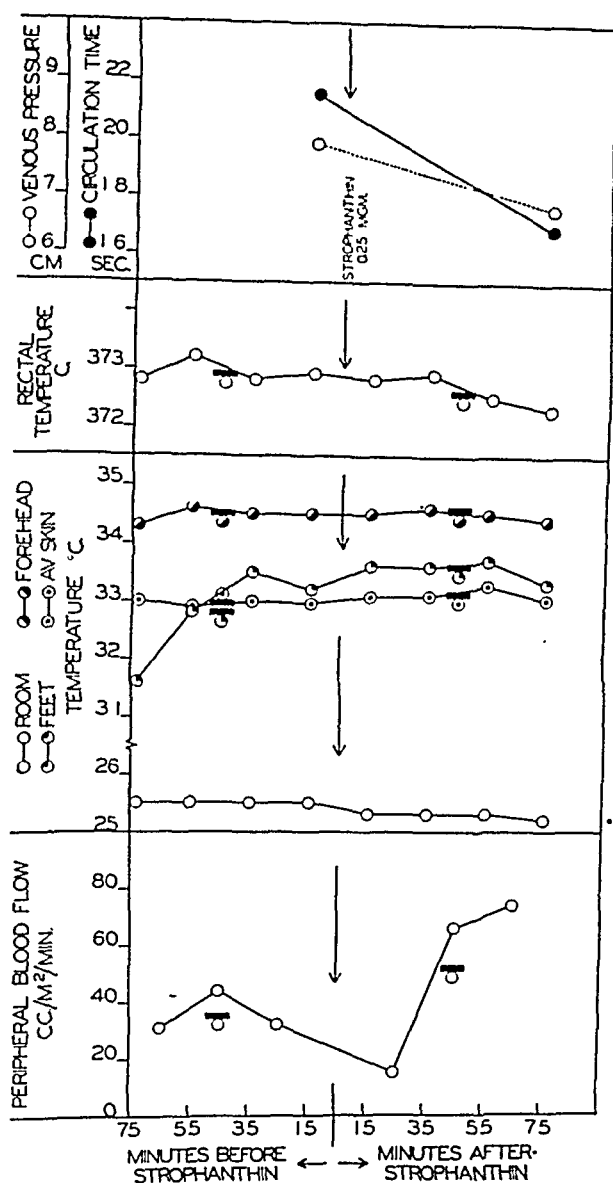
Fig 1.—In this figure are recorded the data relating to D.S. showing the effect on the peripheral blood flow and skin and on the skin and rectal temperatures, venous pressure and circulation time, of the administration of 0.25 mg. of strophanthin K. The averages of the measurements before and after injection of the drug are shown by appropriate symbols attached to a black bar.

18. Taylor, F. A.; Thomas, A. B., and Schleiter, H. G.: A Direct Method for the Estimation of Venous Blood Pressure, Proc. Soc. Exper. Biol. & Med. **27**:867, 1930.

in case there had been any emotional response to the venipuncture and the bitter taste of the dehydrocholic acid.

OBSERVATIONS

There were 11 observations of 9 patients relating to strophanthin K. The results for 1 patient (D.S.) serve to illustrate the effects of this
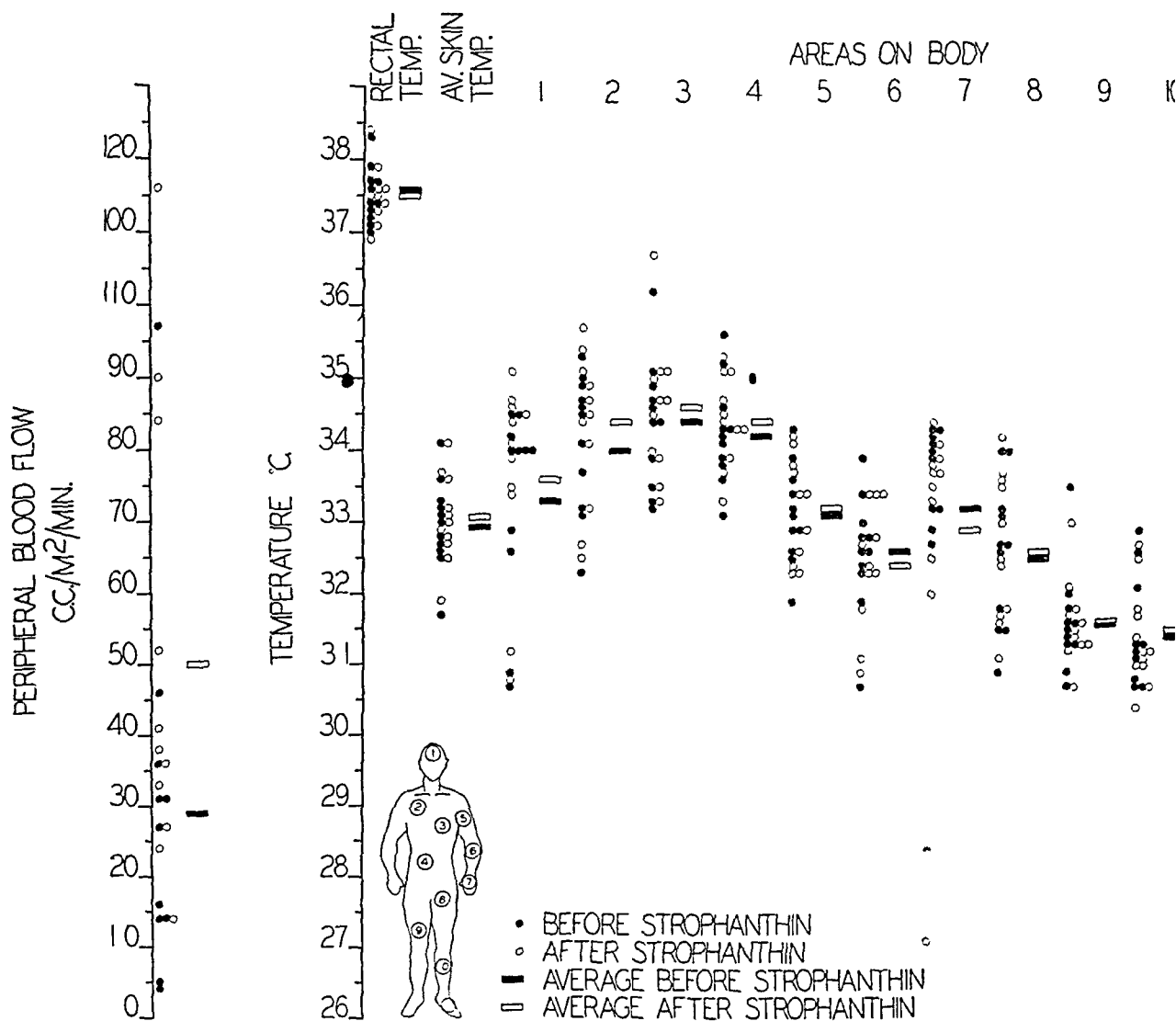
Fig. 2.—In this figure are recorded the data relating to patients given strophantin K. The closed circles indicate the average of each patient's measurements before, and the open circles the average of the measurements made on the same morning after, the administration of strophanthin K. The averages of all the patients before and after the administration of strophanthin K are represented by the solid and open bars respectively.

drug (table 1, fig. 1). The results for all patients are shown in the table and in figure 2.

The Peripheral Blood Flow, Skin and Rectal Temperatures in Congestive Heart Failure.—The average of the peripheral blood flow

for all patients during heart failure was 32 cc. per square meter per minute, that is to say, in the normal range (the table and fig. 2), as compared to 33 cc. per square meter per minute [19] for normal subjects at the same room temperature of 25 C.[20] The rectal temperature was higher than normal, and the average skin temperature was slightly warmer than normal. The temperature of the forehead (area 1) and lower part of the thigh and leg (areas 9 and 10) was slightly cooler than normal, while for all the other areas it was warmer than normal, except for the hand (area 7), which was the same.

The Effects of Strophanthin K on Peripheral Blood Flow, Rectal and Skin Temperatures in Congestive Heart Failure.—The peripheral blood flow was 36 cc. per square meter per minute, in short, in the normal range [21] in D. S., although this patient had congestive heart failure (fig. 1). The rectal temperature was elevated to 37.29 C. (99.37 F.), and the average weighted skin temperature was slightly increased, 32.96 C. (91.29 F.). After the injection of 0.25 mg. of strophanthin K intravenously the peripheral blood flow increased, the rectal temperature fell, the average weighted skin temperature rose and the feet became warmer. The average peripheral blood flow during the sixty-five minutes after injection was 52 cc. per square meter per minute, while the maximum of 74 cc. per square meter per minute was attained sixty-five minutes after injection. The heart rate became slower, the circulation time fell from twenty-two seconds to seventeen seconds and the venous pressure, which was not elevated, fell from 80 mm. to 68 mm.

The results for all the patients are plotted in figure 2 (see also the table). The averages for all the patients showed that the peripheral blood flow increased from 29 cc. per square meter per minute to 50 cc. per square meter per minute after injection, and the average maximal effect over the period of the observations was 71 cc. per square meter per minute for the sixty-four minute period. The rectal temperature fell. The average weighted skin temperature and temperature of the upper part of the body rose slightly.

The Effects of Digitaline Nativelle on Peripheral Blood Flow and Rectal and Skin Temperatures in Congestive Heart Failure.—The effects of giving 1.2 mg. of digitaline Nativelle intravenously were

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19. This figure is lower than in the original paper because only one measurement concerning each patient was averaged.

20. Stewart, H. J.; Haskell, H. S., and Evans, W. F.: The Peripheral Blood Flow and Other Observations in Coarctation of the Aorta, Am. Heart J. **28**:217, 1944.

21. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow Under Basal Conditions in Normal Male Subjects in the Third Decade, Am. Heart J. **26**:67, 1943.

similar to those following the giving of strophanthin K, except that over the time observations were made the increase in peripheral blood flow was less noticeable and the effects were slower in appearing (see the table). The peripheral blood flow increased from 37 cc. per square meter per minute to 49 cc. per square meter per minute. The average maximal peripheral blood flow was 65 cc. per square meter per minute for one hundred and fourteen minutes after injection, as compared with 74 cc. per square meter per minute for sixty-four minutes after the giving of strophanthin K (see the table). There was for this group, after the use of digitaline Nativelle, a slight rise in rectal temperature, a very slight rise in average weighted skin temperature and no significant change in the temperature of the individual areas of the body except of the feet, which was increased. In this group of patients during failure the peripheral blood flow was higher than in the strophanthin K group, and the average weighted skin temperature higher and the rectal temperature lower. This group included 2 patients (M. O'S. and K. H.) who had no signs of heart failure at the time these observations were made.

We have compared the effects of strophanthin K and digitaline Nativelle for 2 patients (M. H. and E. P., table 1). For one, E. P., observations made at comparable times after injection of the two drugs showed that strophanthin K induced its effects more rapidly than did digitaline Nativelle (see the table).

COMMENTS

These observations have shown that during heart failure the peripheral blood flow is in the normal range as compared with the peripheral blood flow in normal subjects at the same environmental temperature.[20] The average weighted skin temperature of the body was slightly increased. The rectal temperature was elevated. The forehead was slightly cooler than normal. The hands were of the same temperature and the feet warmer than those of normal persons at the same room temperature. Sixty-four minutes after the injection of strophanthin K the peripheral blood flow increased; for the whole group the maximum effect on peripheral blood flow was recorded sixty-four minutes after injection, when it was 71 cc. per square meter per minute (see the table). When all the observations for all patients for corresponding times are averaged and plotted, a curve is shown for the initiation of effects on the peripheral blood flow (fig. 3). On this curve the maximal increase to 66 cc. per square meter per minute was obtained in sixty minutes for strophanthin K. The average weighted skin temperature increased, and the rectal temperature fell. On the average, the temperature of most of the areas of the body increased and of the hands and forearms decreased slightly (fig. 1). At this time there was slowing

of the heart rate, the circulation time was shorter and the venous pressure less.

How can these results be correlated with the other known effects of digitalis? In observations of Stewart and Cohn, the cardiac output was decreased and the heart dilated in dogs whose hearts had been made to fibrillate.[22] Forty-five minutes after tincture of digitalis had been given intravenously, decrease in size of the heart and increase in cardiac output occurred. Digitalis induced similar results in a dog [22] in which, by ingestion of bromide, edema had been induced, which was associated with decrease in cardiac output and increase in cardiac
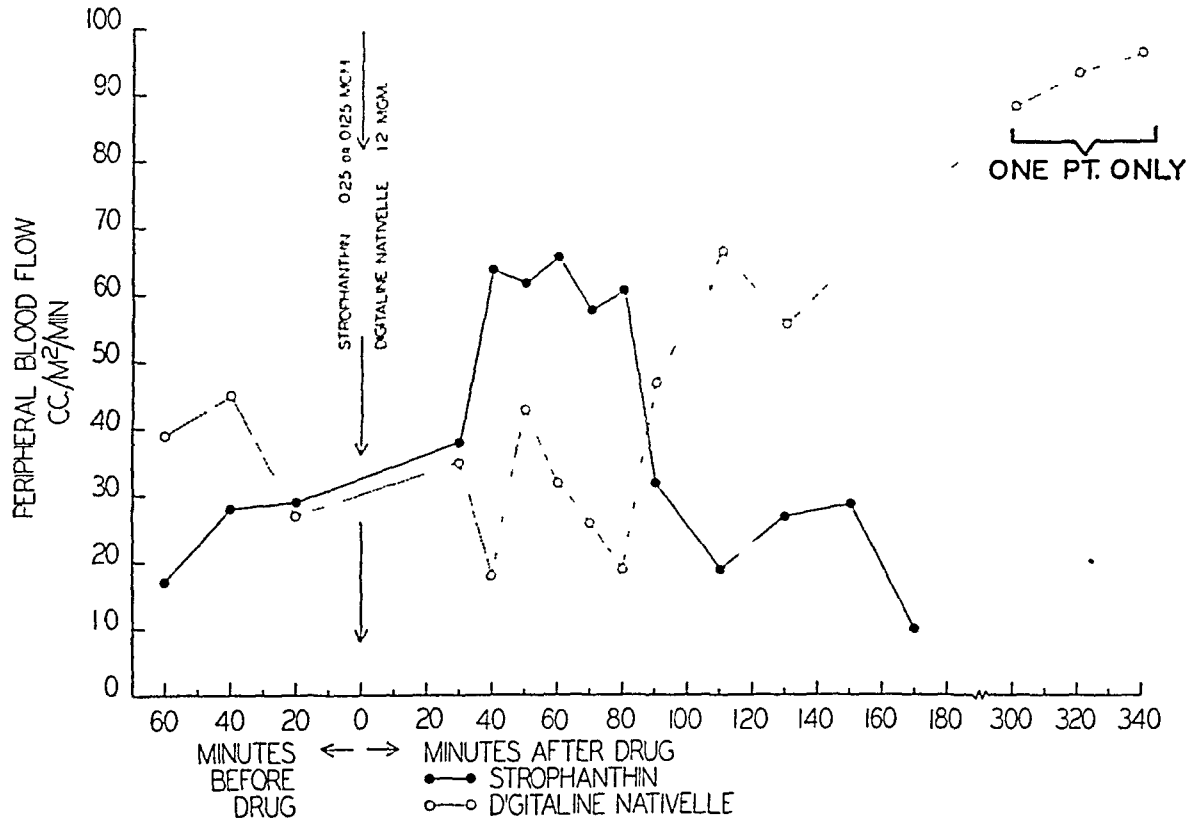
Fig. 3.—In this figure are recorded the effects on peripheral blood flow of strophanthin K and digitaline Nativelle. All the measurements of all patients receiving each drug were averaged for each time interval before and after injection, so that a curve is obtained. The last 3 circles on the digitaline Nativelle curve represent measurements of only 1 patient.

size, since increase in cardiac output and decrease in cardiac size occurred twenty-four hours after digitalis had been given intravenously. Similar results were recorded by Stewart, Deitrick, Crane and

22. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: II. The Effect on the Output of Hearts of Dogs Subject to Artificial Auricular Fibrillation, J. Clin. Investigation **11**:897, 1932.

Thompson [23] when the drug was given by mouth to patients with auricular fibrillation. Also in patients with heart failure to whom the drug was given by mouth, increase in output and decrease in size of the heart [6] could be detected as early as nine hours after administration. Moreover, in normal subjects when the drug was given by mouth, effects on cardiac output and on cardiac size [2] were observed as early as nine hours. Stewart and Cohn [2] and Stewart [24] and others [5] have shown that the volume output of blood from the heart is decreased during heart failure and that as early as nine hours after digitalis has been given by mouth an increase in cardiac output has occurred. In short, in all of these there is ample evidence that the volume output of blood is decreased in congestive heart failure and that the effect of digitalis is to increase the volume of blood expelled by the heart. These effects may now be correlated with those relating to peripheral blood flow. At a time when the cardiac output is low during failure or as a consequence of auricular fibrillation,[25] the peripheral blood flow is in the normal range; in short, in the face of the decreased output of blood from the heart, a normal amount is, nevertheless, allotted to the peripheral circulation. The average skin temperature of the body is warmer than normal. The rectal temperature is elevated in heart failure. One explanation of these events is as follows: During heart failure the volume of blood allotted to the peripheral circulation in unit time is in the normal range, but it moves so slowly in a distended vascular bed in which there is an increased volume of circulating blood [26] that it is probably insufficient to eliminate heat from the body; the rectal temperature rises as a consequence. Other adjustments, such as increase in heat lost in moisture by way of the lungs, are brought into use and prevent to some extent a greater rise in internal temperature. With the exhibition of strophanthin K, the peripheral blood flow increases within sixty-four minutes, the average weighted skin temperature increases, and the rectal temperature falls slightly. In short, with the increase in cardiac output which has been brought

23. Stewart, H. J.; Dietrick, J. E.; Crane, N. F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms: Observations Relating to (Part I) Rhythms Associated with Rapid Ventricular Rate, and to (Part II) Rhythms Associated with Slow Ventricular Rate, J. Clin. Investigation 17:449, 1938.

24. Stewart, H. J.; Deitrick, J. E.; Watson, R. F.; Wheeler, C. H., and Crane, N. F.: The Effect of Valvular Heart Disease on the Dynamics of Circulation, Am. Heart J. 16:477, 1938. Stewart, Deitrick, Crane and Wheeler.[3] Stewart and others.[4]

25. Stewart and Cohn.[2] Stewart, Deitrick, Crane and Wheeler.[3] Stewart, Deitrick, Crane and Thompson.[23]

26. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, J. Clin. Investigation 16:851, 1937.

about by strophanthin K, an increased amount is available and is distributed to the periphery of the body; with more blood brought to the periphery the average skin temperature and temperature of most of the areas of the skin becomes higher. With the increased amount of blood available to the skin surface for radiation of heat the rectal temperature falls.

The highest peripheral blood flow after the administration of strophanthin K was recorded sixty-four minutes after the drug was given, while the highest after the administration of digitaline Nativelle occurred later, namely one hundred and fourteen minutes afterward. There were no significant changes in the peripheral blood flow sixty-four minutes after the administering of digitaline Nativelle. The difference in the time at which the effects of strophanthin K and digitaline Nativelle are evident is shown in figure 3, in which all the measurements of peripheral blood flow at corresponding times before and after injection are averaged and plotted for each of the two drugs. It is apparent that the peripheral blood flow increases forty minutes after injection of strophanthin K and remains elevated for eighty minutes after injection, and then decreases. On the other hand there are no significant changes after the administration of digitaline Nativelle at this time, but the increase begins about ninety minutes after injection and is still present one hundred and thirty minutes afterward. In 1 patient in whom observations were made five hours after injection the peripheral blood flow was still higher than the control levels.

These results following the exhibition of digitalis bodies are different from those recorded by Eichna and Taube,[8b] who found that the return of venous pressure and ventricular rate to normal was not accompanied with a significant alteration in the volume of blood flow to the resting hand and calf; they used a plethysmographic method. The method my colleagues and I have used records the average peripheral blood flow allotted to the periphery of the whole body in cubic centimeters per square meter per minute for a depth of 1 cm., rather than the flow in isolated areas.

In 2 patients (M. H. and E. P.) the effects of strophanthin K and of digitaline Nativelle were compared. The results were similar to those in which the large groups of individual patients were compared.

The basal metabolic rate was increased in many of these patients, which is not uncommon in heart failure.[27] When the peripheral blood flow is plotted against the corresponding basal metabolic rate before and after the administering of digitalis, a rough linear correlation is apparent, in that the higher peripheral blood flow occurred in those patients with the higher basal metabolic rate and the lower peripheral

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27. Stewart, H. J., and Jack, N. B.: The Basal Metabolic Rate in Organic Heart Disease, Am. Heart J. **19**:738, 1940.

blood flow occurred in those with the lower basal metabolic rate. In short, patients with a basal metabolic rate in the normal zone had lower peripheral blood flow, and the ones with a higher basal metabolic rate had higher peripheral blood flow, but not as high as it would have been for the corresponding increases in basal metabolic rate which occur in hyperthyroidism.[28]

Our results with respect to skin temperatures for the areas of the body are unlike those of Steele and Cohn [1ab] in that in our patients with heart failure we found no definite change on the average in the local temperature, although in certain patients this was the case. They measured skin temperatures in fewer areas than we did. If our patients had exhibited more pronounced heart failure the results might not have been so divergent. On the other hand, Abramson, Fierst and Flachs [7] found the blood flow to edematous limbs within the range of that obtained in normal subjects, results comparable to ours, namely, that the blood flow allotted to the whole periphery is in the normal range for the environmental temperature. The rectal temperature was elevated. This, we think, is due to the inability of the body, with the volume of blood allotted to the periphery—although this is normal in amount—to eliminate enough heat by this route. The blood moves at a slower velocity because of the increased size of the vascular bed and increased volume of blood. For the higher level of basal metabolic rate the amount is insufficient to eliminate heat adequately, and rise in rectal temperature occurs. Peripheral cyanosis is one visual evidence of the decrease in velocity of blood flow in heart failure. A linear correlation was not apparent when the average weighted skin temperature was plotted against the corresponding rectal temperatures.

SUMMARY

The peripheral blood flow has been measured in patients exhibiting congestive heart failure before and after the administration of strophanthin K and digitaline Nativelle intravenously. A modification [10] of the Hardy-Soderstrom method was used.[13] Measurements of rectal and of skin temperature were recorded. Electrocardiograms were taken at appropriate intervals. Circulation time and venous pressure were measured in order that there might be other data to correlate with the measurements of the peripheral blood flow. These effects have been discussed in relation to another known effect of digitalis bodies, namely, their effect on cardiac output. It appears that:

1. The amount of blood flow allotted to the whole periphery of the body is in the normal range during heart failure as compared with

28. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Hyperthyroidism, Am. Heart J. **20**:715, 1940.

the amount in normal subjects at the same environmental temperature. Although the volume output of blood from the heart is decreased in heart failure, there is no apparent restriction in the amount of blood allotted to the peripheral circulation.

2. The average weighted skin temperature is slightly increased in heart failure; the forehead is slightly cooler, and the feet are slightly warmer than normal; the temperature of the other areas of the skin is in the normal range.

3. Even though the same amount of blood is allotted the peripheral circulation in heart failure, it is insufficient, because of its slowed velocity in a vascular tree that is dilated, to maintain an adequate elimination of heat in the face of the metabolic demands, so that the internal temperature of the body (rectal temperature) rises.

4. After the administration of strophanthin K intravenously, the peripheral blood flow increases. The volume output of blood from the heart having been increased by digitalis, more blood is now available for the peripheral circulation. With the allocation of more blood to the periphery, the temperature of the skin rises and the feet become warmer still. The body can now lose more heat by way of the skin and its internal temperature (rectal temperature) falls slightly but does not usually reach normal levels over the intervals studied.

5. Similar results were observed following the intravenous injection of digitaline Nativelle.

6. The effects were observed from forty to sixty minutes after the administration of strophanthin K, but were slower, namely eighty minutes, in appearing after the administration of digitaline Nativelle. This difference in time in which effect on peripheral blood flow occurs is in agreement with observations of others, which showed that, molecule for molecule, ouabain initiated effects more rapidly and digitaline Nativelle more slowly.

PATENT DUCTUS ARTERIOSUS WITH SUBACUTE BACTERIAL ENDARTERITIS

Diagnosis and Indications for Operation

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LIGATION of the patent ductus arteriosus was first proposed in 1907, by Munro.[1] He had seen a healthy infant die of this cardiac anomaly. Based on the observations at autopsy and other anatomic studies, he described in detail an operation for ligation of the ductus, although he himself had never performed one on the living. He stated, in general, "The one cardiac valvular lesion which is relatively speaking superficial" could be attacked "by a short surgical route"; the ductus "could easily be surrounded with ligature." He "doubted whether it would materially hasten a fatal issue in case the diagnosis were not confirmed." The operation was advised for failure of the circulation.

Not until thirty-one years later was the first attempt to ligate the patent ductus arteriosus reported (Graybiel, Strieder and Boyer).[2] Their patient had superimposed subacute bacterial endarteritis. The purpose of the operation was to destroy the bacterial vegetation by obliteration of the ductus. An anterior mediastinotomy was performed. The ductus was plicated. They were unable to obliterate the lumen completely. The patient succumbed on the fourth postoperative day of acute dilatation of the stomach.

The first successful ligation of the patent ductus arteriosus was reported by Gross and Hubbard[3] in 1939. Their patient was a 7½ year old girl with uncomplicated patent ductus arteriosus. The indications for operation were beginning embarrassment of the circulation and hope of prevention of subacute bacterial endarteritis. The operation was a transpleural one, carefully and skilfully worked out by Dr. Gross.

● The first recovery from subacute bacterial endarteritis on patent ductus arteriosus effected by surgical obliteration of the ductus was

1. Munro. J. C.: Ligation of the Ductus Arteriosus, Ann. Surg. 46:335. 1907.

2. Graybiel, A.; Strieder, J. W., and Boyer, N.: An Attempt to Obliterate the Patent Ductus Arteriosus in a Patient with Subacute Bacterial Endoarteritis, Am. Heart J. 15:621 (May) 1938.

3. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus, J. A. M. A. 112:729 (Feb. 25) 1939.

reported by Touroff and Vesell in 1940.[4]   Those reporting opera-
tions on uncomplicated patent ductus arteriosus at that time considered
the presence of subacute bacterial endarteritis a contraindication to
operation.   The danger of increased bacteremia and embolization was
mentioned.   Ligation of the ductus in the case was proposed by one
of us (H. V.) with the idea simply that it would eliminate factors
(forceful blood current through the ductus) which were favorable to
the development and maintenance of the bacterial endarteritis.   The
operation, in which the technic of Gross was used, was followed by
prompt subsidence of the bacterial infection.

During the five years which have elapsed since this report, endar-
teritis in the ductus arteriosus gradually came to be accepted as an
indication for surgical obliteration of the patent ductus.   The operation
was performed by many surgeons both here and abroad.   Results were
most gratifying in that a condition which previously was almost 100 per
cent fatal became curable in the majority of cases.

During the past few years it has been demonstrated that penicillin
therapy is effectual in cases of subacute bacterial endocarditis, includ-
ing those with underlying patent ductus arteriosus.[5]   It is therefore
timely to consider the indications for surgical measures in the light of
the five years of experience with operation and recently with penicillin.

After it was demonstrated that ligation or excision of the ductus
could terminate the superimposed bacterial endarteritis,[6] it was felt
that all patients in whom the diagnosis was definitely established should
be operated on promptly with two exceptions.[7]

These exceptions were, first, patients with important associated con-
genital cardiac anomalies for which the ductal shunt was a vital com-

4. Touroff, A. S. W., and Vesell, H.:   Subacute Streptococcus Viridans
Endarteritis Complicating Patent Ductus Arteriosus, J. A. M. A. **115**:1270 (Oct.
12) 1940.

5. (*a*) Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.:   Combined
Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, J. A. M. A.
124:144 (Jan. 15) 1944. (*b*) Dawson, M. H., and Hobby, G. L.:   The Clinical
Use of Penicillin; Observations in One Hundred Cases, ibid. **124**:611 (March 4)
1944.   (*c*) MacNeal, W. J.; Blevins, A., and Poindexter, C. A.:   Clinical
Arrest of Endocarditis Lenta by Penicillin, Am. Heart J. **28**:669 (Nov.) 1944.
(*d*) Paullin, J. E., and McLaughlin, C. J.:   The Treatment of Subacute Bacterial
Endocarditis with Penicillin, Ann. Int. Med. **22**:475 (April) 1945.   (*e*) Spink,
W. W., and Hall, W. H.:   Penicillin Therapy at the University of Minnesota
Hospitals: 1942-1944, ibid. **22**:510 (April) 1945.

6. Touroff, A. S. W.; Vesell, H., and Chasnoff, J.:   Operative Cure of Sub-
acute Streptococcus Viridans Endarteritis Superimposed on Patent Ductus Arteri-
osus: Report of the Second Successful Case, J. A. M. A. **118**:890 (March 14) 1942.

7. Touroff, A. S. W., and Vesell, H.:   Experiences in the Surgical Treatment
of Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus
Arteriosus, J. Thoracic Surg. **10**:59 (Oct.) 1940.

pensatory mechanism and, second, patients with evidence of extension of bacterial vegetations beyond the ductus and pulmonary artery, particularly those with involvement of the left side of the heart. These exceptions will be considered later.

The establishment of the correct diagnosis naturally was a prerequisite to operation. That this was accomplished with little error is revealed in the fact that in 140 operations on the ductus (33 with subacute bacterial endarteritis) reviewed recently by Shapiro and Keys,[8] the diagnosis was in error in only 2. This group consisted only of cases in which operation for ductal closure had been performed. Data are not available concerning the uncertainty and inaccuracy of diagnosis in the large number of cases without operation.

·*Many observations contribute to the diagnosis of patent ductus arteriosus* and subacute bacterial endarteritis. The usual history is that the patient was not a "blue baby." The presence of a cardiac murmur from infancy was almost always known. Cyanosis did not occur except with pulmonary or cardiac complications.

The most helpful diagnostic sign was the characteristic train-in-a-tunnel machinery murmur. Heard best just left of the sternum between the second and third intercostal spaces, it is loud, low pitched, rumbling and harsh. It grows louder during systole, reaching its maximum intensity in late systole and early diastole, and continues through most of diastole. A short silent period may be recorded in the phonocardiogram just before the first sound. When once heard the murmur can hardly be mistaken. The transmission of this murmur is quite uniform. The systolic component is well transmitted over most of the front and back of the chest, left and right; the interscapular transmission was described long ago by François-Franck.[9] The murmur can be heard in the left axilla and in the neck. The diastolic component, and consequently the continuous murmur as a whole, my colleague and I have found quite regularly to have a characteristic area of transmission, in the shape of a rectangle (fig. 1) with the following borders: upper, left clavicle; lower, fourth intercostal space; right, midsternum; left, the midclavicular line. The striking difference in size of the small area of transmission of the diastolic component from the very much larger area for the systolic is suggestive of a different source or origin for each component. Laubry and Pezzi[10] developed

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8. Shapiro, M. J., and Keys, A.: The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention: A Clinical Series of Fifty Cases and an Analysis of One Hundred and Thrity-Nine Operations, Am. J. M. Sc. **206**:174 (Aug.) 1943.

9. François-Franck, M.: Sur le diagnostic de la persistance du canal artériel. Gaz. hebd. de méd. **25**:588, 1878.

10. Laubry, C., and Pezzi, C.: Traité des maladies congenitales du cœur. Paris, J. B. Ballière et fils, 1921.

some evidence to indicate that the diastolic component was produced by pulmonary insufficiency, while the systolic was produced in the ductus.   There have been many explanations for the murmur.   Some cases of patent ductus arteriosus even beyond childhood will undoubtedly be missed and patients deprived of the benefits of operation if, as recently suggested, the diagnosis not be made without the presence of a continuous machinery murmur.   In some instances the murmur
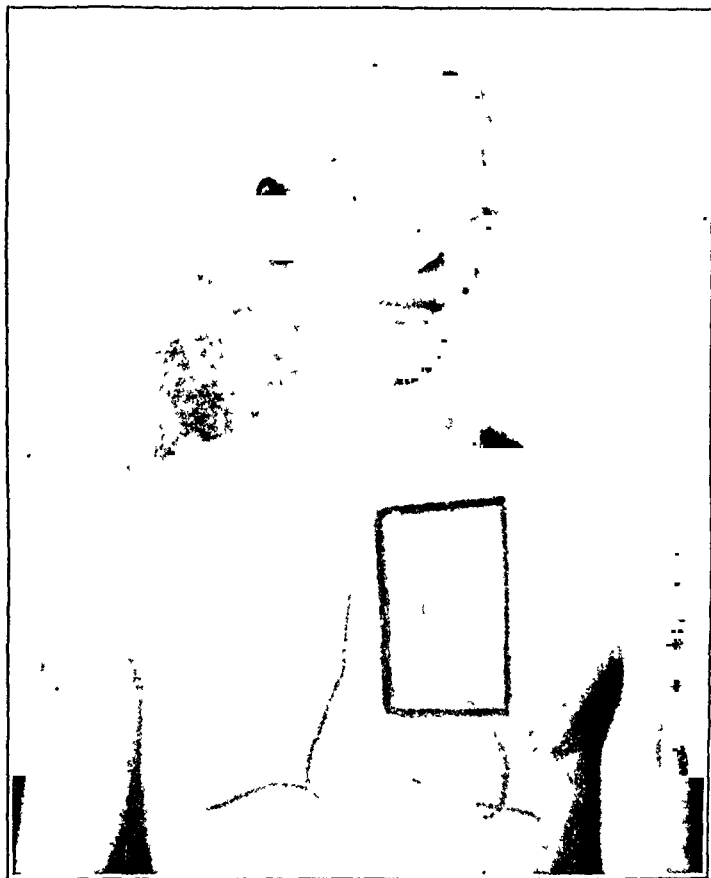
Fig. 1.—Rectangular area of transmission for the diastolic component of the continuous murmur of patent ductus arteriosus. (The subject with the outline of a normal heart on the chest is from Roesler, "Clinical Roentgenology of the Cardiovascular System." The illustration is reproduced by permission of Charles C Thomas, Publisher, Springfield, Illinois.)

is limited to systole.   Abbott [11] found this to be so in 30 per cent of her 92 cases.   It is not so common in adults.   In 1 of our adult patients in whom this was the only murmur consistently heard, operation revealed a very short but wide ductus.   The systolic was also the

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11. Abbott, M. E.:   Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936, p. 32.

only murmur heard in 2 adults with uncomplicated patent ductus arteriosus. Rarely, a murmur is lacking.[12]

A thrill can almost always be felt over the area of the pulmonic valve; it may be brought out by having the patient bend forward and hold the breath in deep expiration.

The roentgenogram is frequently helpful in diagnosis, especially for those cases in which the labeling continuous murmur is lacking. The prominence of the pulmonary artery (roentgen ray cap of Zinn), with increased hilar and pulmonary markings (together referred to as Assmann's sign), occurs in over one half the cases. On fluoroscopy increased pulsation of the pulmonary artery was noted and considered of diagnostic value long ago by Wessler and Bass,[13] who also pointed out that, in contrast, the prominent pulmonary artery in mitral stenosis pulsates little. The roentgenokymogram reveals the great amplitude of the waves produced by the increased pulsations of the pulmonary artery (fig. 3), also some increase in the excursion of the left ventricular border.

Angiocardiography can be of considerable value in diagnosis. A characteristic and possibly pathognomonic abnormality has been pointed out by Sussman, Grishman and Steinberg.[14] In the left oblique position a small but definite bulge was found in the aortic shadow at the site of the aortic infundibulum of the ductus. This bulge occurred in 26 of their 27 cases. The size of the cardiac chambers may be normal. Angiocardiography should be employed in all doubtful cases, particularly those in which operation is contemplated.

The electrocardiogram is usually normal and is sometimes helpful in establishing the diagnosis by ruling out other conditions in which diagnostic changes are expected. There may be slight or moderate left axis deviation. Slight right axis deviation is infrequent and was seen only once in about 15 cases. Pronounced right axis deviation is strong evidence against the presence of patent ductus arteriosus as an isolated or primary defect.

The arterial blood pressure is altered rather characteristically in most cases. The diastolic pressure in the brachial artery is commonly about 20 to 30 mm. of mercury below normal, as in patients with a

12. (*a*) Goodman, E. H.: Report of a Case of Patent Ductus Arteriosus Botalli with a Study of the Cases Heretofore Published, Univ. Pennsylvania M. Bull. **23**:509 (Dec.) 1910-1911. (*b*) Shapiro, M. J.; Keys, A., and Violante, A.: Clinical and Physiological Analysis of Twenty-Three Patients with Persistent Patent Ductus Arteriosus, Internat. Clin. **4**:148 (Dec.) 1941.

13. Wessler, H., and Bass, M. H.: Persistent Ductus Botalli and Its Diagnosis by the Orthodiagraph, Am. J. M. Sc. **145**:543 (April) 1913.

14. Sussman, M. L.; Grishman, A., and Steinberg, M. F.: Newer Concepts in the Diagnosis of Congenital Heart Disease, Am. J. Dis. Child. **65**:922-936 (June) 1943.

large arteriovenous aneurysm. The systolic pressure is normal, usually a low normal. Typical blood pressures are systolic, from 100 to 125 and diastolic, from 45 to 60 mm. of mercury.

Bohn [15] has called attention to a response of the arterial blood pressure to exercise which he believed diagnostic. A control reading of the blood pressure is taken with the patient standing. The blood pressure cuff is left on the arm, and the patient exercises by taking ten knee bends (or their equivalent). A pressure reading is made immediately after. The diagnostic sign is the occurrence of a substantial reduction of the diastolic pressure following exercise. Elevation of the systolic pressure is noted as in normal subjects. Bohn warned that if more than a minute elapsed after the exercise is completed the characteristic response may be missed. In 1 of his patients, a 17 year old girl with patent ductus arteriosus and without cardiac decompensation, the resting blood pressure was 130 mm. of mercury systolic and 60 mm. diastolic; immediately after ten knee bends it became 200 systolic and 20 diastolic; then 165 systolic and 50 diastolic and 135 systolic and 50 diastolic, and, one minute after, 120 systolic and 60 diastolic. Aortic insufficiency. severe hyperthyroid heart and cardiac effects of high fever should be excluded. Bohn found the sign of considerable aid in the diagnosis of patent ductus arteriosus. Lewicki [16] has also found the sign of aid and has modified it slightly by adding a second series of ten knee bends to the exercise. In an 18 year old patient with patent ductus arteriosus and questionable cardiac decompensation he obtained the following blood pressure changes: control, blood pressure in the arm, 125 mm. of mercury systolic and 50 diastolic; after 10 knee bends, 165 systolic and 0 diastolic, and after ten more, 205 systolic and 0 diastolic. The blood pressures in the legs (tibialis posticus) were: control, 162 systolic and 90 diastolic; after ten knee bends, 173 systolic and 110 diastolic, and after ten more, 175 systolic and 110 diastolic. The diastolic pressure in the legs was raised rather than lowered after the exercise.

In our attempt to apply the test of Bohn, definite positive responses were obtained in several patients with uncomplicated patent ductus arteriosus. In the patients with endarteritis the test was not as satisfactory. Because of the inability of the patient to perform the regular test exercise other physical effort, allowing the patient to remain in bed, was substituted. Kicking back and forth against resistance and alternate sitting up and lying down were tried to the point of some fatigue of the patient. Little reduction in the diastolic pressure after

15. Bohn, H.: Ein wichtiges diagnostisches Phänomen zur Erkennung des offenen ductus art. Botalli, Klin. Wchnschr. **17**:907 (June 25) 1938.

16. Lewicki, E.: Zur Diagnostik des offenen Ductus arteriosus Botalli, Wien. klin. Wchnschr. **50**:1029 (Dec. 13) 1940.

the physical effort occurred: 122 mm. of mercury systolic and 46 diastolic before exercise and 144 systolic and 38 diastolic after; and 84 systolic and 48 diastolic before exercise and 90 systolic and 45 diastolic after, in 2 patients with ductal endarteritis in whose cases the diagnosis was confirmed at operation.

The test may be useful in the differential diagnosis of patent ductus arteriosus from other congenital (or acquired) cardiac lesions. In a patient with an interatrial septal defect, corroborated by angiocardiography, a negative response was recorded: when the patient was standing, blood pressure in the arm was 120 mm. of mercury systolic and 80 diastolic; after fifteen [17] knee bends, 140 systolic and 90 diastolic; at another time, when the patient was standing the pressure was 120 systolic and 70 diastolic; after fifteen knee bends, 124 systolic and 70 diastolic, and after fifteen more, 144 systolic and 70 diastolic. This suggests that a pronounced positive response with lowering of the diastolic blood pressure to close to zero, as often occurs after the second series of knee bends in patients with patent ductus arteriosus, should favor the diagnosis of patent ductus arteriosus against that of interatrial septal defect, in situations in which the two conditions are considered. This differential diagnosis is at times difficult, and any aid is desirable.

One adult with an interventricular septal defect, a diagnosis corroborated by angiocardiography, had the following response to the test exercise: the blood pressure, standing position, was 122 systolic and 84 diastolic; after ten knee bends it was 130 systolic and 70 diastolic, and after ten more, 132 systolic and 60 diastolic. A slightly positive reaction to the test would not be of value in the differential diagnosis of these two conditions. A strongly positive reaction to the Bohn test with reduction of the diastolic pressure to near zero would favor the diagnosis of patent ductus arteriosus.

On the basis of some or all of the mentioned clinical and laboratory features—history, murmur, reaction of blood pressure, together with the roentgenogram, roentgenokymogram and angiocardiogram—the diagnosis of patent ductus arteriosus should be made correctly in practically all cases.

The diagnosis of the superimposed subacute bacterial endarteritis was made on clinical and laboratory observations similar to those in cases with underlying acquired heart disease. Unexplained fever of one week or more in patients with patent ductus arteriosus requires that such a diagnosis be carefully considered or be made tentatively. Symptoms encountered early were irritability, weakness, anorexia, feeling of warmth with perspiration, chills, cough and loss of weight.

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17. Fifteen instead of ten knee bends were used for more agile or robust young adults.

Recent dental extractions and pregnancy were occasionally associated and possibly connected. Petechiae were not common early. Systemic embolization occurred much later than in the ordinary subacute bacterial endocarditis. Pulmonary embolization was more frequent. Red blood cells were found in the urine infrequently. The blood culture contained the organism early and at times contained 100 to 400 colonies per cubic centimeter of blood. Finally, repeated blood cultures of the organism should be obtained for corroboration of the diagnosis of subacute bacterial endarteritis.

When the diagnosis of patent ductus arteriosus with subacute bacterial endarteritis was established, the possible presence of contraindications to operation had to be determined. There were two contraindications of importance. The first was associated congenital cardiac anomalies for which the patent ductus arteriosus was a vital compensatory mechanism. Experience has shown that such associated anomalies are most uncommon after infancy and if present would be expected to be revealed in cyanosis from associated pulmonary stenosis, and the signs of coarctation of the aorta—aortic stenosis or atresia if one of these conditions were also present. Fortunately such associated lesions were not noted in our experience and were extremely rare in the cases of others when operation was performed. Septal defects, atrial or ventricular, need not be a contraindication to the operation.

The second contraindication for operation is extension of infection beyond the ductus and especially to the left side of the heart. It has been argued that operation on the ductus could have no effect on bacterial vegetations in the aorta, in the mitral or aortic valves and probably not even on vegetations in the pulmonary valve. This conclusion cannot be wholly accepted, for it is far from proved. If it is true, the high percentage of cures by operation would be difficult to explain. Early reports based on necropsies in cases of patent ductus arteriosus with subacute bacterial endarteritis revealed that the infection, though starting at the pulmonic orifice of the ductus, had spread considerably beyond the ductus in most cases. Review of the first 19 reported cases (Schlaepfer 1926)[18] disclosed only 3 in which the bacterial infection was limited to the pulmonary artery and ductus; in the remaining 16 there was involvement of the valves: mitral alone, 5; aortic, 13 (9 with mitral); tricuspid, 1 (with mitral and aortic), and pulmonic valve, 9. Blumer and McAlenney[19] in 1931 reviewed 28 cases, and found the following involvement of valves: aortic valve, in 14 cases; pulmonary

18. Schlaepfer, K.: Chronic and Acute Arteritis of Pulmonary Artery and of Patent Ductus Arteriosus, Arch. Int. Med. **37**:473 (April) 1926.

19. Blumer, G., and McAlenney, P.: Relationship of Patent Ductus Arteriosus to Infectious Processes in the Duct Itself, in the Pulmonary Artery, the Aorta and the Heart Valves, Yale J. Biol. & Med. **3**:483 (July) 1931.

valve, in 14 cases; mitral valve. in 9 cases: tricuspid valve, in 4 cases. and multiple valves in 40.7 per cent of the cases. Gordon and Perla,[20] also writing in 1931, stated that up to that time there were only 4 recorded instances of patent ductus arteriosus with subacute bacterial endarteritis in which the valves were spared, and they added the fifth. Abbott [21] stated that in her collected series of 92 cases of primary patent ductus arteriosus there were 27 with mycotic endarteritis. in 23 (85 per cent) of which there was involvement of the valves of the heart and in only 4 (15 per cent) there was not. Hubbard, Emerson and Green.[22] in a review of 39 cases reported up to 1939. noted only 14 (35 per cent) without valvular involvement. If extension of the infection to the valves would destroy the chances of cure by ductal ligation. then. on the basis of the cited necropsy statistics, recovery should not occur in 65 to 85 per cent of the cases. This, however, was not borne out in the series of cases in which operation was performed. Of the 28 patients who survived operation 20. or 72 per cent, recovered.' Were the valves involved in 65 to 85 per cent of the cases in the necropsy series and in only 28 per cent of the patients operated on? In the series in which operation was performed the duration of the endarteritis was generally shorter. and therefore less extension of the bacterial vegetations would be expected. Observations on 3 patients who died at operation or shortly thereafter did show less extension. In 1 patient who died at operation [7] a few pinpoint verrucae were found on the pulmonary valve in addition to the vegetations in the ductus and pulmonary artery. In the 2 others there was no involvement of the valves. One [2] of these patients died four days after operation; vegetations were found in the pulmonary artery 1 cm. above the right leaflet of the pulmonary valve. In the third [7] case the patient died at operation. The ductus was destroyed at operation. Two firm vegetations, each about 3/16 inch (0.48 cm.) in diameter. were found in the pulmonary artery immediately opposite the opening of the ductus. The duration of the endarteritis prior to operation · in these 3 patients was three and one-half months, four months and five months. The difference in duration of bacterial infection between the series with operation and the necropsy series undoubtedly accounts for freedom of the valves from infection in many of the former. However. because of the high

20. Gordon, H., and Perla. D.: Subacute Bacterial Endarteritis of the Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonic Stenosis, Am. J. Dis. Child. **41**:98 (Jan.) 1931.

21. Abbott, M.. in Nelson's Loose-Leaf Medicine. New York. Thos. Nelson & Sons, 1942, vol. 4. p. 269.

22. Hubbard. J. P.; Emerson, P.. and Green. H.: Indications for the Surgical Ligation of a Patent Ductus Arteriosus. New England J. Med. **221**:481 (Sept. 28) 1939.

incidence (65 to 85 per cent) of valve involvement in the cases in which there was necropsy it seems likely that in some of the 20 (72 per cent) patients who recovered after operation the valves too were involved. In support of this inference is the long duration of infection (seven to ten months) in several patients operated on successfully, and also the short period of time after onset of infection that valvular involvement may occur—three and a half months in the first of the 3 cases just cited. The presence of signs of embolization in the systemic circuit in some of the surgically treated group also suggests that there were vegetations on the valves or in the aorta. Recovery even after involvement of the valves may be explained in the following manner. First, there is some natural tendency for vegetations on valves to heal. Pathologic specimens of infected valves in most cases of subacute bacterial endocarditis commonly show evidence of some degree of healing.[23] The occurrence of healing is also documented by the cases (1 to 3 per cent) of spontaneous recovery.[24] Second, in patent ductus arteriosus with subacute bacterial endarteritis bacterial infection of the valve develops on a normal valve instead of one with underlying rheumatic or other disease. Healing should be less difficult. Ordinarily subacute bacterial endocarditis rarely develops on normal valves. The third and most important reason for healing of the valvular infection is the elimination of the current through the ductus and infection in it by the surgical procedure. Thus a feeding source for other sites (valves) of cardiac infection is eradicated. A forceful blood current with strong eddies and turbulence appears to be necessary for the development and maintenance of bacterial vegetations in the heart or in arteriovenous aneurysms with subacute infection with Streptococcus viridans. The forceful currents and eddies favor the production of fibrin necessary for the protection of the bacterial growth, so that bactericidal polymorphonuclear leukocytes[25] may not reach and destroy the bacteria. It is meaningful that subacute bacterial endocarditis is common in mitral insufficiency, aortic insufficiency, patent ductus arteriosus and ventricular septal defects, but uncommon in tight mitral stenosis or in atrial septal defects. The presence of forceful blood currents and eddies produced by strong ventricular contraction in the former may be the reason. Elimination of the forceful whirling current of the ductus by operation is curative at least in part through this mechanism.

23. Libman, E.: A study of the Endocardial Lesions of Subacute Bacterial Endocarditis with Particular Reference to Healing or Healed Lesions, Am. J. M. Sc. **144**:313 (Nov.) 1912.

24. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, New York, Oxford University Press, 1941, p. 81.

25. Friedman, M.; Katz, L. N., and Howell, K.: Experimental Endocarditis Due to Streptococcus Viridans, Arch. Int. Med. **61**:95 (Jan.) 1938.

The presence of petechiae has been considered a contraindication to operation. There are two important reasons that this need not be so. First, petechiae may be purpuric or may be due to a toxic endotheliitis rather than to bacterial embolization.[24] Second, in some cases in which they are caused by bacterial emboli, the bacteria may have had their source in the vegetations in the ductus and may have been forced through the dilated pulmonary vascular bed by the increased pulmonary vascular pressure to reach the systemic circulation. Even should they be derived from valvular vegetations recovery could still be possible, as a result of the obliteration of the ductus. Besides the better chance for a normal valve to heal there would be the added benefit from a potent chemotherapy now available on a lesion rendered less formidable after obliteration of the ductus. Petechiae or other evidence of systemic embolization and left-sided cardiac involvement therefore should not constitute an absolute contraindication to operation.

There is no longer any doubt that penicillin is curative of the bacterial infection in many cases of subacute endocarditis caused by S. viridans. Loewe, Dawson, MacNeal, Paullin, Spink[5] and others have adequately demonstrated this. Subacute bacterial endarteritis with patent ductus arteriosus has responded at least as well as with other complications (Spink).[5c] The percentage of cure is somewhat over 50 and probably higher with larger dosage. The problem in endarteritis with patent ductus arteriosus is whether penicillin without operation should be the treatment of choice or whether operation should be performed also, and if so when.

There are three circumstances in which operation is indicated. First, operation is indicated in cases in which the bacteria obtained on blood culture were found by test in vitro to be insensitive to penicillin; organisms in this category would include gram-negative bacilli, most higher bacteria and some strains of alpha hemolytic streptococcus which are resistant to concentrations of penicillin obtainable in the blood stream. Greater availability of the drug now permits the development of high concentrations in the blood and should substantially reduce the number of the last group. Thirty million units per day have been administered, and, a concentration of 60 Oxford units per cubic centimeter of blood reached.[26]

Second, operation is indicated for those patients in whom the bacterial infection has been going on for a rather long time. Just how long the time limit should be would be arbitrary. About three months should be a suitable time, but this would depend in large part on the condition of the patient. This second group would include cases in which the bacteria present are sensitive to penicillin;

26. Loewe, L.: Personal communication to the author.

these patients would also receive penicillin. Reasons for prompt operation in these patients would be to avoid extension of the bacterial invasion to other parts of the heart, particularly to the left side of the heart, the mitral and aortic valves, where eradication of the infection would be more difficult. With delay too, the possibility of serious unpredictable complications becomes greater. Cerebral, visceral and peripheral embolization occurs without warning, at almost any time, and all these complications are serious and frequently fatal. Also of considerable importance is the increase in inflammation in and around the ductus with resultant increase in friability and with firm adhesions of the tissues as the infection is prolonged. If chemotherapy, which would take additional time—possibly weeks—should prove unsuccessful, then because of the delay greater danger of hemorrhage would be placed on the operation than necessary.

A third type of case which requires surgical treatment is the following: The bacterial organism is sensitive to penicillin, but for various reasons, after a trial period of several weeks, the response to treatment is not satisfactory. There may be an initial clearance of the blood stream and disappearance of symptoms and signs, but relapse takes place shortly. Relapse may be only in the form of a return of the positive blood culture, with little or no fever. Such a case is the one reported later in this article. In that case the imminence of cardiac failure, which in itself is an indication for obliteration of the patent ductus, made the decision to operate less difficult. The imminence or presence of cardiac failure in any case of patent ductus arteriosus with subacute bacterial endarteritis favors the decision to operate promptly so that the operation necessary for correction of the circulatory defect may also be curative of the endarteritis. Penicillin, of course, should be administered simultaneously in cases in which the bacteria are sensitive.

The following three considerations should be carefully weighed when the surgical treatment is proposed. The first is the operative mortality. In the hands of a patient and capable surgeon of the chest this may not be much more than for operation on the noninfected ductus, if performed early in the course of the infection. The operative mortality is about 8.5 per cent for uncomplicated cases and 15 per cent for those with subacute bacterial endarteritis [12a]; it is less with greater experience and an improvement in technic. The second is that life expectancy in patients with patent ductus arteriosus even without infection is considerably below normal without operation. The average age of the patients in Abbott's series of fatal cases was only 24 years. Though this would be higher if living patients were properly included and infants excluded, it would still be much below normal. The third is the benefits and length of life attained

after operation. This of course remains to be determined. The first patient with subacute bacterial endarteritis cured by the surgical treatment [4] is still well and at regular work five years after the operation. Another patient with the same condition [6] is well and at regular work four years after the operation.

REPORT OF A CASE

History.—F. S., a native-born white woman aged 25 years, single, a secretary, was admitted to the medical service of Beth Israel Hospital Jan. 22, 1945. One of three children, she was not a "blue baby." A cardiac murmur was first noted at the age of 2 years. At school, high school and college she indulged in activities requiring ordinary physical effort, such as stair climbing, without undue fatigue or breathlessness. However, she was advised to abstain, and did, from games involving strenuous physical effort. She was always physically well developed and well nourished.

About two years before admission she had influenza; then for four weeks she received digitalis medication for supposed cardiac failure. For the two years following this attack of influenza she did not feel well, becoming more easily fatigued and short of breath on less effort. Three weeks prior to admission she became ill with a sore throat, swelling of the cervical lymph nodes and fever. Infectious mononucleosis was suspected, and a course of sulfonamide therapy was given. She began to lose weight; the fever persisted, and she was then sent to the hospital.

Examination.—The patient was well developed, well nourished, and weighed 120 pounds (54.4 Kg.). She did not appear acutely ill. The temperature was 102.6 F., the pulse rate 130, and the respiratory rate 26 per minute. There was no dyspnea or cyanosis. Petechiae were not seen on the conjunctivas, throat, trunk or extremities. Several cervical lymph nodes posteriorly were moderately enlarged and tender. Teeth were not visibly carious. A slight postnasal drip was present. Prominent pulsations were visible in the vessels of the neck near the clavicle. A systolic thrill was felt in the jugulum. The heart appeared to be slightly enlarged. A rather forceful apex impulse was palpable just outside the midclavicular line in the fifth intercostal space. Here the first sound was moderately loud, accompanied and followed by a systolic murmur of 2 plus intensity (6 plus maximum); the second sound was slightly accentuated. Over the second intercostal space just left of the sternum there was a systolic impulse, of moderate force, and a purring thrill which occupied most of systole and diastole. Over this area a continuous, loud, machinery murmur was heard—intensity 4 to 5 plus. The systolic component was well transmitted to the apex, the aortic area, the right and left interscapular areas, the bases of both lungs and the neck on both sides. The diastolic component was heard well only in the rectangular area described in figure 1: above to the clavicle, below to the fourth intercostal space, to the midsternum on the right and to the midclavicular line on the left. The pulmonic second sound was slightly accentuated, the aortic second normal. There was no evidence of cardiac failure. Circulation time, measured with sodium dehydrocholate, was twelve seconds, and venous pressure was 95 mm. of water. The lungs were clear; the liver was not palpable; the spleen was felt 1 to 2 fingers below the costal margin. There was no clubbing of the fingers. The blood pressure in the standing position was 116 mm. of mercury systolic and 46 diastolic; after ten feeble knee bends it was 118 systolic and 30 diastolic, and after ten more 116 systolic and 24 diastolic. Four weeks later blood

pressure in the standing position was 144 systolic and 70 diastolic, and after ten knee bends 150 systolic and 24 diastolic; leg pressure (at knee) was 200 systolic and 126 diastolic; after ten knee bends it was 250 systolic and 140 diastolic.

Laboratory Data.—A teleroentgenogram revealed the heart to be a little enlarged in the region of the left ventricle. There was slight prominence of the pulmonary artery arc with straightening of the left cardiac border (fig. 2), and moderate increase in hilar and peribronchial markings. Kymographic examination showed wide pulsations of the pulmonary artery (fig. 3). The electrocardiogram revealed a left axis deviation. The R wave in lead I was high, 21 mm.; the R wave in lead II was 3 mm.; the S wave in lead III was 13 mm., and the angle alpha was plus 8 degrees; T waves were erect. The chest lead, IV F, was normal. A
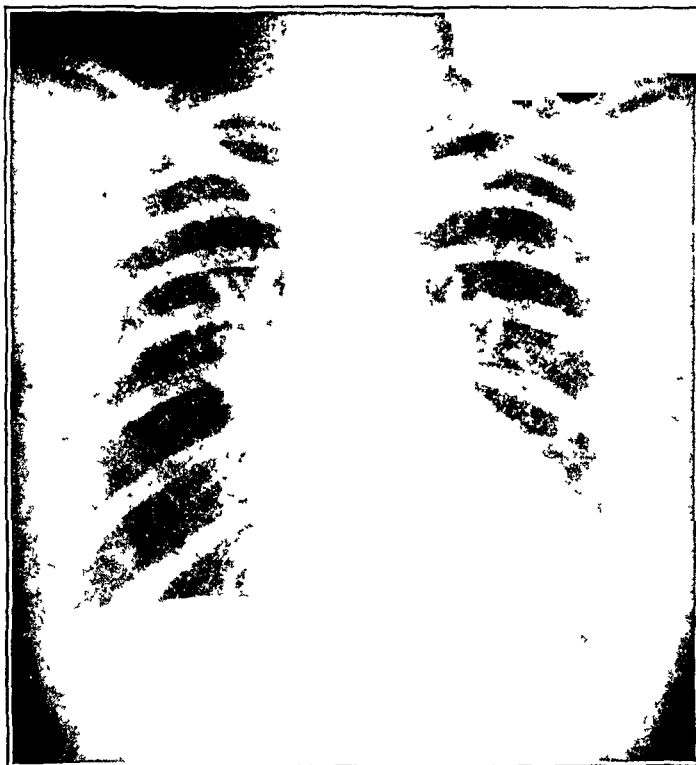
Fig. 2.—Teleroentgenogram showing slight prominence of pulmonary artery, some increase in size of the left ventricle and increase in hilar and peribronchial markings.

phonocardiogram (fig. 4) revealed a continuous murmur over the pulmonic area. There was a short silent period just before the first sound. The specific gravity of the urine was 1.020; reactions to tests for albumin and dextrose were negative. An occasional red blood cell was seen in the low power field. No casts were found. The blood contained 4,150,000 red cells per cubic millimeter; hemoglobin content was 11.5 Gm. per hundred cubic centimeters of blood. There were 12,000 white cells, of which 76 per cent were polymorphonuclear leukocytes, including 7 per cent "staff" cells; 20 per cent were lymphocytes, 4 per cent large mononuclear cells. The erythrocyte sedimentation rate was 50 mm. in one hour. Reactions to the Wassermann, Kline and Kahn tests were negative. The heterophile antibody reaction was negative on admission and also twenty days later. A blood culture

taken the morning after admission revealed 82 colonies of alpha hemolytic streptococcus or S. viridans per cubic centimeter of blood. The following day, January 24, another blood culture was taken, and 150 colonies per cubic centimeter grew out.

The diagnosis of patent ductus arteriosus with complicating subacute bacterial (S. viridans) endarteritis was made. Because of the good general condition of the patient, good nutrition, absence of signs of cardiac failure and the short duration of the infection, it was decided to treat the patient medically with penicillin rather than by immediate operation. The medical treatment was less formidable and, according to reports at the time, very hopeful. Tests in vitro revealed the
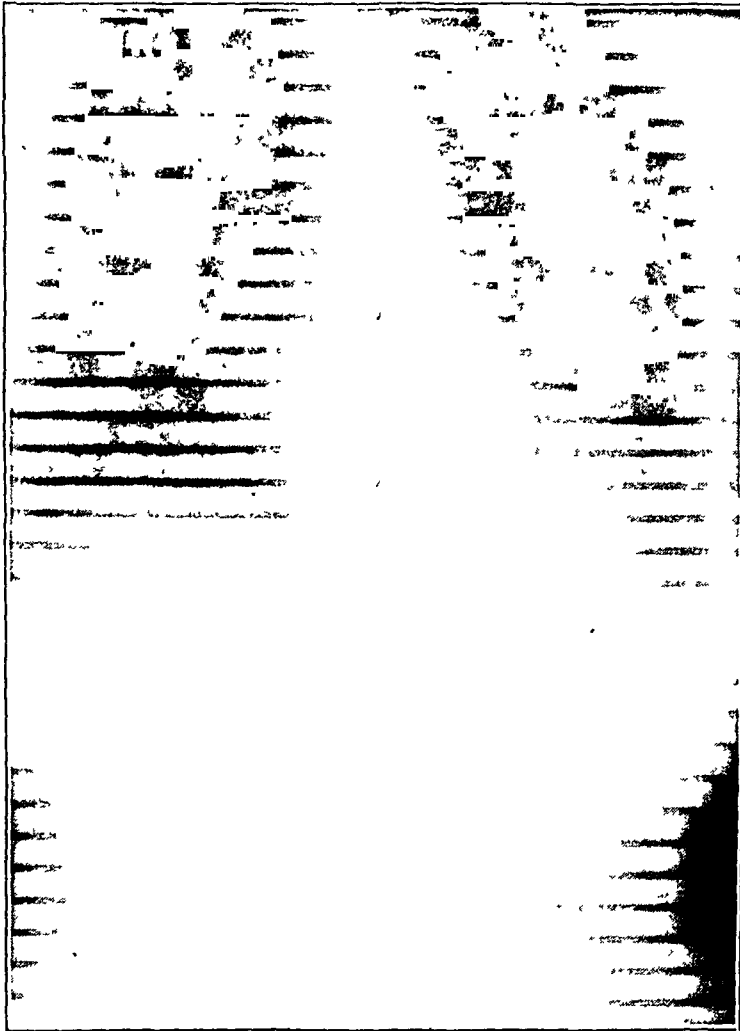
Fig. 3.—Roentgenokymogram showing some increase in pulsations of the pulmonary artery and left auricular region.

organism to be sensitive to as low a concentration as .0125 units of penicillin per cubic centimeter. If satisfactory results were not obtained in about two weeks, operation on the ductus was contemplated. The treatment was started on January 24, with 40,000 units intravenously and a continuous intramuscular infusion. After ten hours the continuous intramuscular infusion was stopped because of pain in the thigh at the site of injection. Eighty thousand units had been given by this route. Intermittent intramuscular administration was then started with 25,000 units every three hours, 200,000 units per day. The patients temperature returned to

normal the day after the penicillin was started and after only 120,000 units had
been given. Her general condition improved, and she said that she felt much
better. After three days of normal temperature the dosage of penicillin was
reduced to 15,000 units and 10,000 units every three hours, alternately. This was
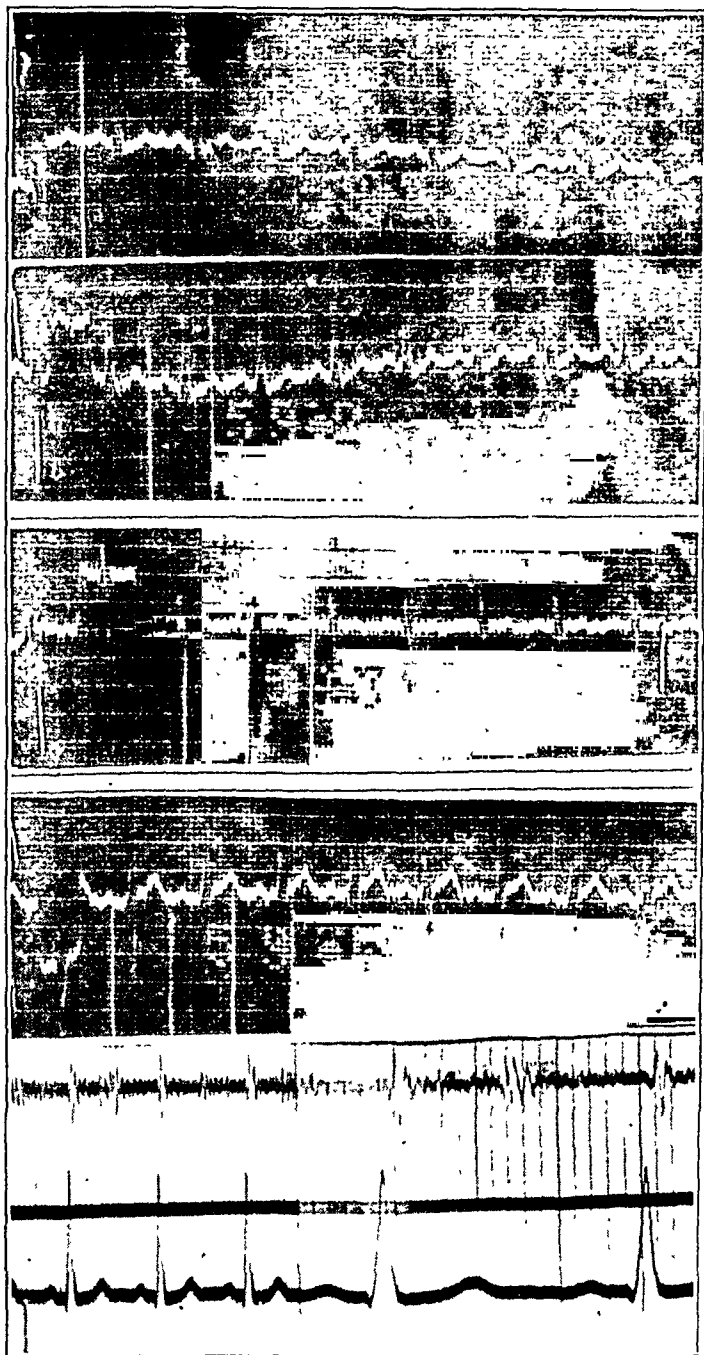
Fig. 4.—Electrocardiogram, leads I, II, III and CF$_{IV}$; left axis deviation,
angle alpha plus 8 degrees. Phonocardiogram with lead I of the electrocardiogram
at the bottom; vibrations due to the continuous murmur occupy all of systole
and diastole with a short silent period before the first sound.

done to conserve the penicillin, the supply at hand having become low. A blood culture January 29, five days after the beginning of treatment, was also sterile. The temperature remained under 100 F. for eleven days, when another blood culture was taken and was reported to contain the organism, 2 colonies per cubic centimeter. The dosage of penicillin was then increased to 20,000 units every three hours for two days through February 9, then to 25,000 units intramuscularly every three hours—200,000 units every twenty-four hours. The temperature rose to between 100 F. and 101 F. daily. The patient began to feel ill again. A blood culture on February 12 revealed 12 colonies per cubic centimeter of blood. It was now quite uncertain whether the penicillin therapy would be successful in clearing the infection, at least in the dosage in which the drug was available for treatment. The blood concentration of penicillin on one determination three hours after injection was less than 0.02 unit per cubic centimeter. It was now three and a half weeks since the beginning of treatment and six and a half weeks since the onset of the infection. It was considered advisable not to delay operation for the following reasons: the uncertainty of cure by penicillin alone; the possibility of extension of bacterial vegetations to the valves, especially on the left side of
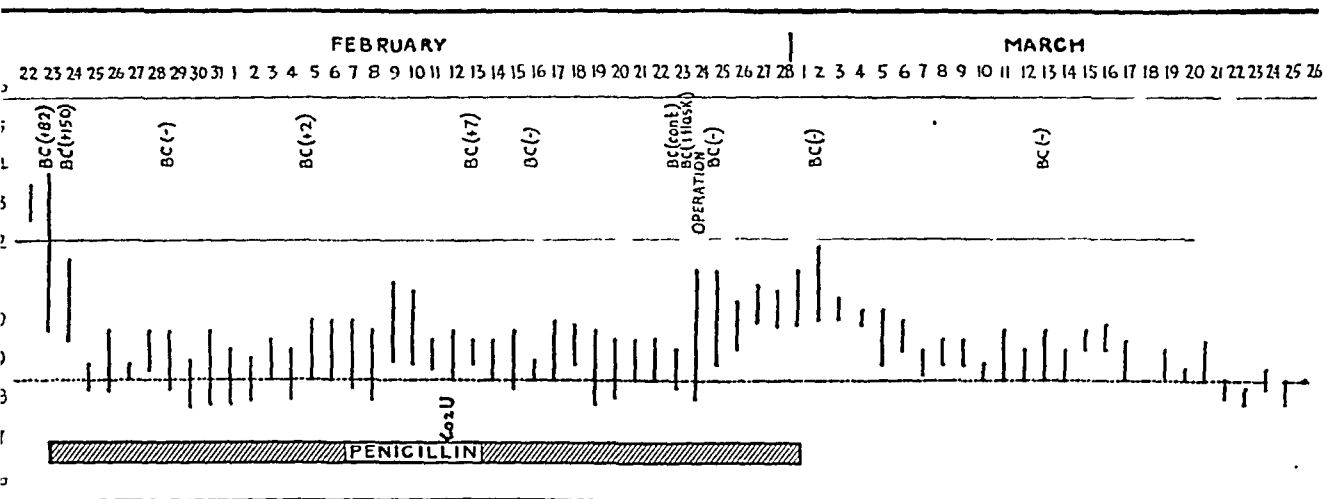
Fig. 5.—Clinical course of F. S. in the hospital. *B. C.* = blood culture; *U* = Oxford units of penicillin.

the heart; the possibility of increasing inflammatory changes in and about the ductus with resultant increased friability of tissues and formation of adhesions making operation more hazardous; the possibility of sudden, unpredictable serious embolization to the brain, viscera or extremities, all of which is more likely to happen as the infection is prolonged. Ligation of the ductus had been shown in the past to produce prompt and permanent clearance of the infection of the blood stream.

Additional indication for obliteration of the ductus was the fact that the patient's circulatory status was threatened by the defect. This was expressed in the increasing shortness of breath the patient had been experiencing during the past two years. Impending cardiac failure being an indication for operation, it was felt that operation might be carried out promptly and so take care of the infection as well as of the circulatory defect.

Accordingly the operation on the ductus was performed on Feb. 24, 1945, by Dr. I. Kross. The posterior lateral approach was chosen for the reasons

mentioned by Dr. Stuart Harrington,[27] who first employed it. The anesthetics cyclopropane and ether were administered by tracheal airway after morphine and atropine had been given hypodermically. The pleural cavity was entered through the bed of the fourth rib. The lung was collapsed and the mediastinal pleura incised longitudinally over the aorta and the pulmonary artery between the phrenic and vagus nerves, exposing the arch of the aorta and the pulmonary artery. The areolar tissue was rather edematous and contained several blackish colored lymph nodes. The ductus was isolated by blunt dissection; all except the posterior surface had been freed when bleeding occurred. The ductus was then clamped, sutured and incised. *The strong thrill completely disappeared. The edges of the mediastinal* pleura were partially brought together with two interrupted catgut sutures; 5 Gm. of sulfanilamide powder was placed in the mediastinum before closing; an equal amount was placed in the pleural cavity before the chest was closed. The lungs were inflated and practically all the air in the pleural cavity expressed.

The postoperative reaction and shock were moderate. The patient received oxygen in a tent; carbon dioxide was given periodically for deep breathing. Blood and isotonic solution of sodium chloride were given, in reduced amounts because of the increased blood volume due to the circulatory shunt. The general systemic reaction and shock were about the same as in patients with whom the anterior approach was used. The machinery murmur completely disappeared. No cardiac murmurs were heard except for sounds of mediastinal emphysema and pericarditis for a few days. About twelve days after operation a short faint systolic murmur could be heard over the area of the pulmonary valve. The diastolic blood pressure rose to normal; the blood pressure was 120 systolic and 80 diastolic. The spleen was no longer palpable.

Penicillin therapy was continued for six days after operation to prevent postoperative infection. The temperature returned to normal after nine days, and it has remained so since. She was allowed out of bed on March 7.

In preoperative blood cultures taken February 5 and February 13 the organism was present. Those taken February 16 and one flask (plates contaminated) taken on February 24 just before operation, as well as all postoperative blood cultures, February 25, March 2, March 13 and March 27, were sterile. There was a complete return of her former sense of well-being, and she gained 4 pounds (1.8 Kg.). She was discharged March 30 to take about one month of rest before returning to work. Last seen on September 12, seven months after operation, she was in excellent condition and had been working regularly.

SUMMARY AND CONCLUSIONS

Indications for the surgical treatment of subacute bacterial endarteritis complicating patent ductus arteriosus were discussed. Correct diagnosis, a prerequisite to operation, and the following features in diagnosis were considered: the murmur, roentgenographic studies, the electrocardiogram and blood pressure tests.

Contraindications to operation considered were associated congenital cardiac anomalies and extension of the bacterial involvement to the left side of the heart. Petechiae and systemic embolization were not believed to be absolute contraindications.

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27. Harrington, S.: Patent Ductus Arteriosus with Bacterial Endarteritis, Proc. Staff Meet., Mayo Clin. **18**:217 (July 14) 1943.

Penicillin therapy of subacute bacterial endarteritis with patent ductus arteriosus was discussed. Operation was believed indicated (1) when the bacteria causing the subacute bacterial endarteritis were insensitive to penicillin; (2) when infection was of long duration, and (3) when a trial with penicillin therapy was not completely successful and final cure was uncertain.

A case of the last type was described. In this case the patient was treated with penicillin and surgical measures with recovery.

PNEUMONIA IN THE AGED

An Analysis of One Hundred Sixty-Six Cases of Its Occurrence in Patients Sixty Years Old and Over

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I N THE forty-seven years that have elapsed since the publication of the third edition of Osler's famous textbook, one familiar paragraph has remained unchanged in all revisions. "Pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old escape those 'cold gradations of decay' that make the last stage of all so distressing."[1] Modern chemotherapy has made it necessary to revise this famous dictum. Today it is almost commonplace of clinical experience to see old persons recover from acute pulmonary infections, in spite of cardiovascular or pulmonary complications, when actively treated with agents such as the sulfonamide compounds and antibiotics such as penicillin, in conjunction with inhalation of oxygen and measures to combat the associated diseases.

In a disease in which the incidence has been reported as high as 2,000 per hundred thousand in persons over 70, compared with an incidence of 640 in the age group of 15 to 20 years,[2] accurate knowledge of its behavior in the aged is essential for the practitioner. Even today textbooks and medical journals contain such designations as "senile," "terminal" and "hypostatic" pneumonia, terms which imply that some cases of pneumonia are essentially due to old age, or to rest in bed, or to antecedent diseases, and not to active infection. Such terms not only are inaccurate but also imply an unjustified hopelessness and induce a feeling of defeatism in the physician. It must be realized that nearly all pneumonias in the aged are primarily infectious in origin, and that

1. Osler, W.: The Principles and Practice of Medicine, ed. 15, New York, D. Appleton-Century Company, Inc., 1944. In the first edition (1892) and the second edition (1895) pneumonia is referred to as "the special enemy of old age." The quotation cited above occurs for the first time in the third edition (1898), where pneumonia is included with the specific infectious diseases instead of with the diseases of the respiratory system, as in the previous editions.

2. Heffron, R.: Pneumonia with Special Reference to Pneumococcus Lobar Pneumonia, New York, Commonwealth Fund, 1939.

the remainder are secondarily so involved. While in the young the presence of pneumonia is readily determined by the symptoms and signs, in the aged associated diseases or atypical features may often dominate the clinical picture and mask the involvement of the lung.

The factors which influence the occurrence and modification of pneumonia in the aged are the general and local changes associated with senescence as well as the high incidence of associated diseases. The local senescent changes include the relative fixation of the thoracic cage due to calcification of the costal cartilages, the loss of elasticity of the pulmonary tissues, the lessened motility of the bronchial cilia and the depression of the cough reflex. The general tissue changes associated with the aging process are gradual desiccation of the tissue, gradual retardation of cell division, diminished power of cell division and of tissue repair, retardation in the rate of tissue oxidation and cellular atrophy.[3] Immunologic changes have been emphasized by Kaufman.[4] The observation of the decline of the isoagglutinin titer in old age and the parallelism between this titer and the ability of the body to form bacterial antibodies led him to attempt to raise this titer and produce active immunization by the use of antigenic pneumococcus polysaccharides. While these measures seemed to lessen the incidence of the disease, there was no effect on the case mortality.

In an effort to clarify some of the problems presented by pneumonia in old persons, we have studied 166 consecutiive cases of pneumonia occurring in patients over 60 years of age from the wards of the Mount Sinai Hospital and the Home for Aged and Infirm Hebrews, covering the period of five and one-half years between Jan. 1, 1940, and June 30, 1945. In 143 of these, or 86 per cent, the clinical diagnosis of pneumonia was confirmed by roentgenologic examination, fluoroscopy or necropsy. One hundred and forty patients received sulfonamide drugs, 9 received penicillin and 2 were treated with both drugs. Four patients received type-specific serum in addition to sulfonamide drugs. The total number who died in the entire series was 33, or 20 per cent of the total. An analysis according to age, sex and outcome is shown in table 1, and according to causative organism and outcome in table 2.

ANALYSIS OF CASES ACCORDING TO AGE, SEX, OUTCOME AND
CAUSATIVE ORGANISM

In table 1 there are 99 men with a mortality of 23 per cent, and 67 women with a rate of 15 per cent. These differences in incidence and outcome are to be considered along with the well known sex

3. Carlson, A. J.: Older Worker, Hygeia 21:338-339 and 375-377 (May) 1943.
4. Kaufman, P.: Studies on Old Age Pneumonia, Arch. Int. Med. 67:304-319 (Feb.) 1941.

differences of later life, such as the greater longevity, the lower incidence
of arteriosclerotic heart disease and malignant neoplasms, and the
greater mental stability of aged women. From this series of cases of
pneumonia one is tempted to postulate an increased resistance to this
type of infection in older women.

The greater number of the cases of pneumonia occurred in persons
aged 60 to 75 years. Although the higher age brackets are less well
represented, there is no correlation between age and mortality, since
the highest rates occurred in men aged 65 to 69 years, and in women

TABLE 1.—*Analysis of One Hundred and Sixty-Six Cases According to Age, Sex and Outcome*

| | Male | | Female | |
Age Groups	Cases	Deaths	Cases	Deaths
60-64	39	6	18	1
65-69	23	10	24	3
70-74	20	4	19	6
75-79	11	2	3	0
80 and over	6	1	3	0
Total	99	23	67	10 166
Death Rate	23 per Cent		14.9 per Cent	

Total Mortality 20 per Cent

TABLE 2.—*Analysis of One Hundred and Sixty-Six Cases in Persons Sixty Years Old and Over According to Cause and Outcome*

	Total	Deaths	Mortality, Per Cent
A. Pneumonia due to specific organisms.			
1. Diplococcus pneumoniae	65	8	12
2. Streptococcus pyogenes	6	0	..
3. Staphylococcus aureus	1	0	..
4. Klebsiella pneumoniae	1	0	..
B. Pneumonia due to filtrable viruses.			
1. Primary atypical ("virus pneumonia")	12	0	..
2. Influenzal (epidemic) pneumonia	1	1	100
C. Suppurative bronchopneumonia (Neuhof)	7	5	70
D. Pneumonia of undetermined origin	73	19	24.6

aged 70 to 74 years. Of the 23 men and women 75 years old and
over only 3 died, yielding a mortality rate of 13 per cent. These figures
may be compared with those of Stahle,[5] who, in reporting on 15,000
cases of pneumonia with a gross fatality rate of 9.19 per cent, included
2,243 persons over 60 years of age, with a mortality rate of 23.99 per
cent. These patients were treated with sulfonamide drugs either alone
or in combination with specific serum.

In table 2 the series is broken down according to cause and outcome.
In Group A, which includes pneumonias due to .specific organisms,

5. Stahle, D. C.: A Clinical Analysis of Fifteen Thousand Cases of Pneu-
monia, J. A. M. A. **116**:440-447 (Feb. 7) 1942.

there are 65 cases due to various types of pneumococci, with 8 deaths, or a mortality rate of 12 per cent. The types, arranged according to frequency and fatality, are enumerated in table 3. Sixteen cases, or 25 per cent of the whole group of pneumococcic infections, were due to Pneumococcus type III; of these, 3 cases were fatal, or nearly 20 per cent. Type XX was found in 3 cases, all of which were fatal; 1 death each occurred from type VII and type VIII infections. Of interest in this connection is the report of Rumreich,[6] who in a nation-wide study of the causation of the pneumonias found that three quarters of all cases were due to pneumococci, and that three quarters of these were due to these types in the order named: I, III, VIII, VII, IV, V, XIV, II, VI and XIX. Although we had only 65 patients with pneumococcus pneumonia, and they were treated with sulfonamide drugs, serum and penicillin, the mortality rate of 12 per cent may be compared with the results of Kaufman,[7] who, using only sulfapyridine for 81 patients

TABLE 3.—*Incidence of Various Types of Pneumococci and Their Relation to Mortality*

Type	No. of Cases	Mortality	Type	No. of Cases	Mortality
I.........	5	0	XV........	1	0
II.........	2	0	XVII........	8	0
III.........	16	3	XIX........	1	0
IV.........	10	0	XX........	3	3
V.........	1	0	XXII........	2	0
VII.........	4	1	XXIV........	2	0
VIII.........	5	1	XXXI........	1	0
IX.........	2	0	XXXII........	1	0
XI.........	1	0	XXXIII........	1	0
XIV.........	2	0	Untyped........	3	0
			Total..........	65	12%

ranging from 50 years to 90 years, recorded a mortality rate of 23.5 per cent. Flippin, Schwartz and Domm [8] studied 1,635 proved cases of all types of pneumococcic pneumonia, occurring in patients of all ages, treated with sulfonamide drugs. The general mortality rate was 10.6 per cent; for patients under 50 years it was 5.7 per cent, while for patients over 50 years the rate was 21.9 per cent.

The cases of streptococcic and staphylococcic pneumonia in this series are too few in number to warrant any generalizations. In the study of the New York City Pneumonia Control Program, Lawrence and Sutliff [9] reported 8 cases of streptococcic pneumonia treated with

6. Rumreich, A. S., and others: A Nation-Wide Study of the Bacterial Etiology of the Pneumonias, Pub. Health Rep. **58**:121-135 (Jan. 22) 1943.

7. Kaufman, P.: Effect and Toxic Effect of Sulfapyridine in Old Age Pneumonia, New York State J. Med. **40**:204-208 (Feb. 1) 1940.

8. Flippin, H. F.; Schwartz, L., and Domm, A. H.: Modern Treatment of Pneumococcic Pneumonia, J. A. M. A. **121**:230-237 (Jan. 23) 1943.

9. Lawrence, E. A., and Sutliff, W. D.: Streptococcus Pneumonia, New York State J. Med. **40**:1233-1235 (Aug. 15) 1940.

sulfonamide drugs, with 2 deaths in patients over 60 years of age, as compared with a former general mortality rate at all ages of 35 to 60 per cent. Keefer, Rantz and Rammelkamp [10] stated that the hemolytic streptococcus causes 3 to 5 per cent of all cases of pneumonia, but that the frequency varies in epidemics. Of their 55 patients, 7 were over 60 years old, and of these 5 died. They emphasized the serious import of bacteremia and heart failure. Staphylococcic pneumonia, according to Gáspár [11] occurs in 75 per cent of the cases in which the patients are in the first decade of life, and is unusual when the patients are over 40 years of age.

Since only 1 case of pneumonia due to infection with Klebsiella pneumoniae is included in our series, attention is directed to the work of Baehr, Shwartzman and Greenspan,[12] who stress the frequency of this pathogen in the biliary and urinary tracts and in the perforative lesions of the abdomen, and its rarity in pneumonia. They deplore the misplaced emphasis of the scientific name of the organism. Small series of cases of pneumonia due to Bacillus Friedländer have been reported by Solomon [13] and by Perlman and Bullowa.[14] The latter emphasize that B. Friedländer pneumonia of the A type occurs predominantly in older persons. In 7 of 29 cases the patients were over 60 years of age, and the 7 cases were all fatal. In 8 cases of B. Friedländer pneumonia of the B type all the patients were under 60 years of age.

Group B of table 2 lists the pneumonias due to filtrable viruses. One case of hemorrhagic necrotizing pulmonary inflammation, characteristic of the fulminating influenzal infections seen in the 1918-1919 epidemic, had a fatal termination. In the primary atypical or "virus" [15] pneumonia group are included 12 cases, none of which were fatal. The benign course of this disease in the aged conforms to the experience

10. Keefer, C. S.; Rantz, L. A., and Rammelkamp, C. H.: Hemolytic Streptococcal Pneumonia and Empyema: Study of Fifty-Five Cases with Special Reference to Treatment, Ann. Int. Med. **14**:1533-1550 (March) 1941.

11. Gáspár, I. A.: A Study of Primary Staphylococci Pneumonias Occurring at the Rochester General Hospital, New York State J. Med. **41**:834-840 (April 15) 1941.

12. Baehr, G.; Shwartzman, G., and Greenspan, E. B.: Bacillus Friedländer Infections, Ann. Int. Med. **10**:1788-1801 (June) 1937

13. Solomon, S.: Primary Friedländer Pneumonia: Report of Thirty-Two Cases, J. A. M. A. **108**:937-947 (March 20) 1937.

14. Perlman, E., and Bullowa, J. G. M.: Primary Bacillus Friedländer (Klebsiella Pneumoniae) Pneumonia, Arch. Int. Med. **67**:907-920 (May) 1941.

15. Reimann, H. A.: Viral Pneumonias, Bull. New York Acad. Med. **19**: 177-182 (March) 1943; Atypical Pneumonia, Viral Pneumonia or Viroid Pneumonia? Correspondence, J. A. M. A. **127**:543 (March 3) 1945.

in all age groups of other clinicians.[16] The diagnosis in our cases was based on the onset and clinical picture, the normal or low white blood cell count, the roentgenologic observations, the absence of pathogenic bacteria from the sputum and the lack of response to sulfonamide drugs. Flippin has warned against making the diagnosis too often and on too little evidence, pointing out that resistance to sulfonamide drugs alone is an inadequate diagnostic criterion. "In a large city hospital, such as the Philadelphia General, we observe a number of so-called sulfonamide-resistant pneumonias that later prove to be cases of tuberculosis, carcinoma, leukemia, etc." [16b]

In group C of table 2 are listed 7 cases of suppurative bronchopneumonia, of which 5 terminated fatally. This type of pulmonary inflammation has been carefully described by Neuhof,[17] and by Neuhof and Thomas.[18] The latter reported 120 cases, in 13 of which the patients were 60 years old and over. The death rate for the whole series was 24.2 per cent (29 deaths). In our experience the diagnosis in the aged may be overlooked clinically and only revealed at necropsy. The pathologic features of disease such as the frequency of purulent foci account for the lack of response to sulfonamide drugs. Neuhof and Thomas described the disease as "a severe bronchopneumonia involving one, several or many portions of the lung or lungs. Substantial portions of bronchopulmonary segments are involved. Spread from primary areas appears to be chiefly by the mechanism of spillover. Varying degrees of suppuration and necrosis occur within the affected segments of the lung, usually with the formation of single or multiple foci of liquefaction within areas of bronchopneumonia. Necrosis is at times outstanding and spectacular." They emphasized the role of these lesions in the lungs in the pathogenesis of empyema, pyopneumothorax and pulmonary abscess. The recovery in 2 cases in our series was aided by bronchoscopic drainage.

In group D of table 2 are listed the cases of pneumonia of undetermined origin, numbering 73 in all, with a mortality rate of 24.6 per cent. This category is unusually large because of the age of the patients. Collection and bacteriologic examination of specimens of sputum are interfered with by the lack of cooperation of the patient, by the death of the patient before an unsatisfactory specimen can be replaced with

16. (a) Plummer, N., and Ensworth, H. K.: Primary Atypical Pneumonia in General Hospitals and in Private Practice, Bull. New York Acad. Med. 20:292-308 (May) 1944. (b) Flippin, H. I.: The Treatment of Primary Atypical Pneumonia, New York Med. 1:11-14 and 20 (March 20) 1945.

17. Neuhof, H.: Suppurative and Necrosuppurative Bronchopneumonia: Their Surgical Aspects, Dis. of Chest 6:299-305 (Oct.) 1940.

18. Neuhof, H., and Thomas, A.: Acute Suppurative Bronchopneumonia, Arch. Int. Med. 75:45-64 (Jan.) 1945.

another, and by misplaced clinical emphasis, since in many cases the pneumonia is first detected on the autopsy table. Many of·the cases listed here were probably due to pneumococci, since the response to sulfonamide therapy was prompt. It is also likely that a certain number of cases of virus pneumonia are included here. In the fatal cases in this group other serious diseases were regularly found in combination with the pneumonia.

CONDITIONS ASSOCIATED WITH PNEUMONIA

Among the conditions most frequently associated with pneumonia in the aged are cardiovascular, pulmonary, nutritional and cerebral diseases. In the cases in which the patients recovered, of which there were 131, we· shall mention only the principal associated conditions. There were 48 patients with arteriosclerotic cardiovascular disease, including 2 with bundle branch block. Eleven patients were admitted with frank congestive heart failure. There were 10 cases of bronchial asthma, 8 of bronchiectasis, 11 with sufficient emphysema to be of clinical significance, 3 cases with cerebral complications and 11 cases of diabetes mellitus. These conditions existed either alone or, more commonly, in multiple combinations with the pneumonia. On the other hand, in the 33 fatal cases, arteriosclerotic heart disease was noted in 20. In 11 of these the patients were admitted with congestive heart failure. There were 3 cases of cor pulmonale and 2 cases of cerebral hemorrhage. There was emphysema of pronounced degree in 9 cases. Included in the fatal group were 6 cases of diabetes and 1 each of exophthalmic goiter, chronic enterocolitis, rheumatic heart disease, bronchial asthma, pulmonary embolism and cirrhosis of the· liver.

In correlating the incidence of these associated conditions with the results obtained, it is immediately apparent that preexisting pulmonary disease is attended with far lower mortality than associated cardiovascular disease or diabetes. Pneumonia may be the factor which initiates heart failure or, occurring during the course of congestive failure, either aggravates the failure or interferes with the response to therapy. Peripheral vascular failure is far commoner than congestive heart failure in young persons and occurs late in the disease. Old persons are often admitted to the hospital with frank congestive failure complicated by an acute pneumonic process. Any infection may diminish tolerance to sugar and precipitate acidosis in diabetes. Likewise elderly persons with diabetes almost invariably show advanced arteriosclerosis affecting many parts of the body. The increased susceptibility of these patients to infections is well known but poorly understood.

The therapeutic results in the presence of complications demonstrate that the associated conditions may be treated successfully along with the pneumonia. In some of the complicated cases with fatal outcome

included in this series, the original illness furnished the substratum for the pulmonary infection, and the patients were admitted in moribund condition. ˙Active treatment of the pulmonary infection and the associated conditions must be undertaken no matter how overwhelming the odds seem to be against recovery.

In addition to the influence of coexisting diseases, the diagnosis of pneumonia in an old person may be obscured by unusual modes of onset and by an atypical clinical course. In the aged these are more frequent and of different types than in younger age groups. The old often have a childlike attitude to disease and do not seek medical aid until the disease process is far advanced. Cases in which symptoms are referred to the abdomen often simulate surgical conditions. In this series there were 5 of this type, admitted at first to the surgical service with signs suggesting inflammation of the gallbladder or intestinal obstruction. Less well known is the so-called "apoplectiform" type of onset stressed by some of the older authors.[19] Here the clinical picture resembles that of a cerebral accident. This may range from evidences of cortical irritation, unilateral weakness, mental confusion, stupor and unconsciousness to actual hemiplegia. These neurologic signs are due either to toxemia or to temporary cerebral circulatory disturbance, since at autopsy no organic cerebral lesion can be shown. There was 1 such case in this series, with deep coma and one-sided twitchings at the beginning of the illness, in which the brain at necropsy was normal.

Complete latency of a pneumonic infection in the aged was first described in 1835 by Hourmann and Dechambre[20] in the dramatic account of the residents of the Salpêtrière, which was popularized in Charcot's famous lectures, "Old women do not even complain of malaise; no one in their dormitories—either among the attendants, housemaids, or neighbors—notices any change in their condition. They get up, make their beds, walk about, eat as usual, and afterward, feeling a little tired, they totter to their beds and expire. . . . The cadaver is opened, and a large part of the pulmonary parenchyma is found suppurating."[21] Aschoff has described a visit to an aged colleague who was apparently in good health. When notified of his demise only two days later, he expected to find evidence of so-called natural death, but postmortem examination revealed a malignant tumor of the thyroid

19. Schlesinger, H.: Die Krankheiten des höheren Lebensalters, Vienna, A. Hölder, 1914, vol. 1, pp. 334-335.

20. Hourmann, M., and Dechambre, R.: Recherches cliniques pour servir à l'histoire des maladies des vieillards, Arch. gén. de méd. 8:405-428, 1835; 9:338-357, 1836; 10:268-296, 1836; 12:27 and 165, 1836.

21. Charcot, J. M.: Leçons sur les maladies des vieillards et les maladies chroniques, Paris, A. Delahaye, 1868; translated by L. Hunt, New York, William Wood & Company, 1881, p. 27.

gland and lobar pneumonia in the stage of gray hepatization.[22]   A recent study of sudden and unexpected natural death by Helpern and Rabson [23] showed that of 2,030 cases, death was due to disease of the respiratory tract in 23.2 per cent, and that in about one sixth of these fatal cases the patients were 60 years old or older.   In their whole series lobar pneumonia was second to disease of the coronary artery in frequency, causing 8.7 per cent of the total of all sudden deaths in which autopsy was done.   Next in frequency were bronchitis and bronchopneumonia (6.5 per cent), pulmonary tuberculosis (3.4 per cent) and pulmonary embolism and infarction (1.6 per cent).

Uncommonly the pneumonia may have a completely afebrile course. We encountered 2 such cases.   A woman of 74 years whose temperature in five days of hospitalization never was more than 99 F., was given chemotherapy because of roentgenologic evidence of pneumonia. Postmortem examination confirmed the roentgenologic observation. The other was a man of 65 years with a long-standing emphysema and cor pulmonale whose temperature during eight days in the hospital rose only once to 100.8 F. and was normal during the remainder of the time.   This patient did not receive chemotherapy.   At necropsy extensive bronchopneumonia was present in both lower lobes; it was believed to be the cause of death.

Due to the fact that cerebral function in the aged is so frequently impaired by arteriosclerosis and parenchymal changes, toxic mental symptoms not infrequently dominate the course of illness to such a degree as to render management difficult.   There were 4 patients in this series, only 1 of whom recovered, a man of 75 years with a blood culture positive for type I pneumococcus.   Another became so uncontrollable that he climbed out of bed, fell and struck his head; he died four hours later in deep coma.   The effect of toxemia on a brain with parenchymal degeneration and impaired circulation resulting from sclerotic vessels may also account for the mild confusional state which may occur after pneumonia in the old, and persist for varying periods of time, ranging from a few days to months.

In the aged the relapsing and recurrent forms of pneumonia are encountered in which the illness may spread over the course of several months.   Such cases have been observed in the Home, pneumonia in one area responding to chemotherapy, with new involvement occurring later on cessation of treatment.   Five or six such acute episodes over

22. Aschoff, L.:   Zur normalen und pathologischen Anatomie des Greisenalters, Berlin, Urban & Schwarzenberg, 1938.

23. Helpern, M., and Rabson, S. M.:   Sudden and Unexpected Natural Death: General Considerations and Statistics, New York State J. Med. **45:**1197-1201 (June 1) 1945.

the course of a few months are not unusual. Finally, at necropsy areas of old organized and recent pneumonia are found, often adjacent areas.

DIFFERENTIAL DIAGNOSIS

To establish the diagnosis of pneumonia in the aged, a careful history and physical examination are essential, but the symptoms, as we have indicated, may be masked, confusing or difficult to elicit. The signs are often entirely unreliable or uninterpretable, even when an extensive involvement is present, having been altered or hidden by the associated diseases or by lack of cooperation on the part of the patient. Sputum and blood cultures can give confirmatory evidence, although their value for specific therapy has become less. Because of the obstacles to accurate physical diagnosis our most valuable aid is the x-ray. That this method is not more widely used is either because facilities are not readily available or because the patient's condition is considered too critical for removal to the x-ray laboratory. More extensive utilization of mobile x-ray units which may be brought to the bedside will lead to greater diagnostic accuracy in the aged. But it is also true that even the roentgenogram may be misleading. Occasionally it may be found that, at the onset, the roentgenogram may be negative, even when physical signs are definitely present. Another exposure, after a short interval, will then show pneumonic infiltration. The following case report and the accompanying roentgenograms show how difficult it may be to differentiate pneumonia and pulmonary infarction.

Pulmonary Infarction.—A man of 85 years was admitted to the infirmary of the Home with pronounced cyanosis, dyspnea at rest, edema of the legs and a temperature of 102 F. There were signs of congestion at the base of the left lung and in the axilla. He was considered to have congestive heart failure and was treated accordingly. A roentgenogram showed what appeared to be a typical infiltration in the lower part of the upper lobe of the right lung and also at the base of the lower lobe of the right lung adjacent to the right cardiac border. As his temperature had become normal and his general condition improved, no chemotherapy was given. A week later a second roentgenogram showed a gradual resolution of the infiltration in the right lung with the appearance of an area of recent infiltration in the upper portion of the lower lobe of the left lung. Eight days later another roentgenologic examination showed the areas in the upper lobe of the right lung to be cleared, with the infiltration in the left side also clearing. Some infiltration persisted in the lower lobe of the right lung. The clinical impression was of a silent broncho-pneumonia complicating congestive heart failure. Four days later he died suddenly. At necropsy an organized infarct was found corresponding to the shadow in the upper lobe of the right lung, a broken-down infarct in the apex of the lower lobe of the left lung and an area of atelectasis in the lower lobe of the right lung (figs. 1, 2 and 3).

This case illustrates but one of the conditions involved in the differential diagnosis of pneumonia in the aged. Space limitations permit only the mention of diseases which may simulate pneumonia, such as

Fig. 1.—Roentgenogram of the chest of an 85 year old man under treatment for congestive heart failure, showing infiltration in the lower part of the upper lobe of the right lung, interpreted as pneumonic in character.

Fig. 2.—Roentgenogram of the chest of the same person, one week later, showing the disappearance of infiltration in the upper lobe of the right lung and the appearance of lesion in upper part of the lower lobe of the left lung.

(1) coronary thrombosis with myocardial infarct and early pulmonary edema, (2) congestive heart failure with or without pulmonary infarct, (3) pulmonary embolism arising often from a silent phlebothrombosis of the lower extremities,[24] (4) pulmonary abscess, (5) bronchostenosis either from foreign bodies or from neoplasms, (6) pulmonary atelectasis of either the lobar (massive collapse) or lobular type, (7) pulmonary neoplasms, both primary and metastatic, (8) metastatic septic foci, (9) pulmonary tuberculosis, (10) bronchiectasis and (11) the chronic lipid pneumonias. Before diagnosing pneumonia in the aged all of the foregoing must be seriously considered and ruled out. The facile diagnosis of pneumonia based on the presence of cough, fever and a few

Fig. 3.—Roentgenogram of the chest of the same patient, eight days later, showing the disappearance of lesions in both the right and the left lung.

moist rales at the bases of the lungs is to be avoided, and every effort must be made to establish a diagnosis based both on the pathologic anatomy and on the bacteriologic examination.

The principal complications other than those connected with the associated diseases are empyema, meningitis and endocarditis. All

24. White, P. D.: Pulmonary Embolism and Heart Disease: Review of Twenty Years of Personal Experience, Am. J. M. Sc. 200:577-581 (Nov.) 1940. Homans, J.: Pulmonary Embolism Due to Quiet Venous Thromboses and Simulating Cardiac and Pulmonary Disease, New England J. Med. 229:309-314 (Aug. 19) 1943. Ask-Upmark, E.: Occurrence of Thrombosis and Pulmonary Embolism in Pneumonia, Acta med. Scandinav. 113:286-303 (March 18) 1943.

recent reports [25] have noted the lower incidence of empyema in all age groups since the advent of chemotherapy. Two cases of empyema were encountered, one of which, in an 84 year old man, is worthy of comment because of the excellent effect of penicillin, administered intrapleurally and intramuscularly.

Empyema.—Patient A. J., an 84 year old man, had noted cough, fever and pain in the chest two weeks previously, which had apparently yielded to sulfonamide medication. When first seen he was cyanotic and dyspneic, with his temperature elevated to 101 F. The peripheral vessels were sclerotic; the pulse was totally irregular, and his heart was enlarged. Because of dulness and distant breath sounds at the base of the right lung, exploratory aspiration of the chest was performed, which yielded thick blood-tinged pus. On culture Pneumococcus type III was isolated, which was found to be one quarter as resistant to penicillin as the standard organism. Intramuscular penicillin therapy, 15,000 units every four hours, was begun. Potain aspiration of the right pleural cavity yielded 200 cc. of purulent fluid, and 30,000 units of penicillin was injected intrapleurally. These procedures were continued daily for one week until a total of 800,000 units intramuscularly and 230,000 units intrapleurally was administered. The gradual clearing of the shadow is of particular interest, since treatment was given for only one week, at which time the purulent fluid obtained from the pleural cavity had become sterile. The patient was observed in the hospital for two weeks after cessation of active therapy. Since he felt well, was entirely afebrile and suffered no discomfort from the residual effusion, he was discharged to his home. Figure 4 *A* shows the effusion at the time of diagnosis, figure 4 *B, C* and *D* at one month, two month and five month intervals. Particular attention is directed to the very gradual resolution of the intrapleural shadow over a period of months.

This result in a man of advanced age is in accordance with the experience of Rudensky, Sprong and Woods [26], Hirshfeld, Buggs, Abbott and Pilling [27] and Healy and Katz,[28] all of whom treated much younger patients. Of decisive importance in our case was the small size of the pleural effusion. Had it been larger, surgical intervention might have been obligatory in order to relieve respiratory embarrassment, even

25. Hurwitz, S., and Stephens, H. B.: Empyema in Children, J. Pediat. **14**: 11-20 (Jan.) 1939. Schwartz, L.; Flippin, H. F., and Turnbull, W. G.: Treatment of Pneumococcic Pneumonia: A Comparative Study of Three Hundred and Fifty-One Patients Treated at the Philadelphia General Hospital, Ann. Int. Med. **13**:1005-1012 (Dec.) 1939. Flippin, H. F.; Schwartz, L., and Rose, S. B.: Comparative Effectiveness and Toxicity of Sulphathiazole and Sulphapyridine in Pneumococcic Pneumonia, ibid. **13**:2038-2049 (May) 1940.

26. Rudensky, H.; Sprong, D. H., Jr., and Woods, C. C.: The Medical Treatment of Acute Empyema, J. A. M. A. **128**:573-577 (June 23) 1945.

27. Hirshfeld, J. W.; Buggs, C. W.; Abbott, W. E., and Pilling, M. A.: The Value of Penicillin in the Treatment of Empyema, J. A. M. A. **128**:577-582 (June 23) 1945.

28. Healy, M. J., Jr., and Katz, H. L.: The Treatment of Empyema Thoracis with Penicillin, J. A. M. A. **128**:568-573 (June 23) 1945.

though the fluid was sterile. The absence of loculation was also a favorable feature. The gradual disappearance of the effusion over a period of months and the excellent reexpansion of the lung are particularly noteworthy.

Until the introduction of the sulfonamide drugs pneumococcic meningitis was almost invariably fatal. The optimal treatment today, as reported by Sweet, Dumoff-Stanley, Dowling and Lepper,[29] consists of intramuscular and intrathecal injections of penicillin combined with
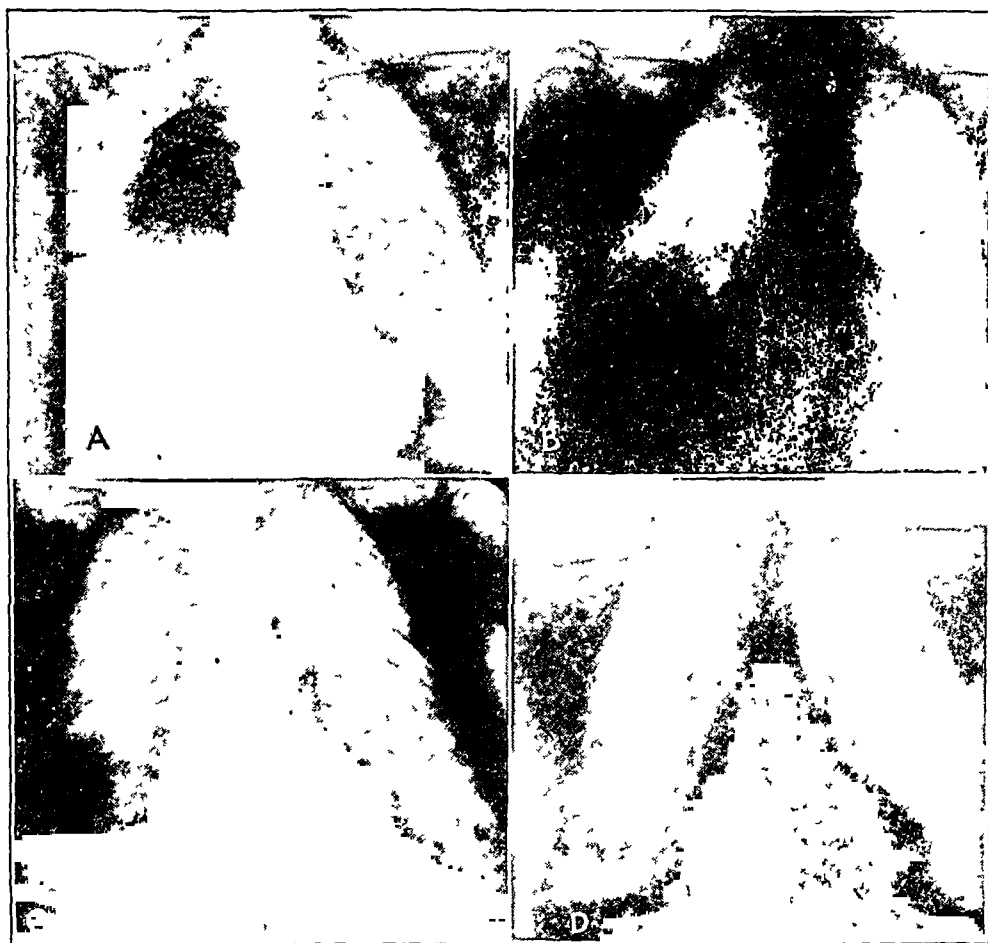
Fig. 4.—A, roentgenogram of the chest of an 84 year old man showing effusion in the right pleura. B, roentgenogram of the chest of the same patient, one month later, after completion of penicillin therapy, showing only slight diminution in size of effusion and small amount of air in right pleural cavity. C, roentgenogram of the chest of the same patient, two months later, showing pronounced diminution in size of effusion. D, roentgenogram of the chest of the same patient, three months later, showing only residual thickening of the right pleura.

the administration of sulfonamide drugs. In their series of 16 cases of pneumococcic meningitis treated with penicillin with and without

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29. Sweet, L. K.; Dumoff-Stanley, E.; Dowling, H. F., and Lepper, M. H. The Treatment of Pneumococcic Meningitis with Penicillin, J. A. M. A. **127**:263-267 (Feb. 3) 1945.

sulfonamide drugs, there were 7 recoveries. Thus, there was a mortality rate of 56 per cent as compared with a rate of 93 per cent in 40 cases of the disease treated only with sulfonamide drugs. Included in our series of pneumonia cases is that of a man aged 74 years suffering from a Pneumococcus type II infection of the meninges as well as of the lungs and blood stream, in which an excellent result was obtained by combined therapy.

Pneumococcic Meningitis.—A man aged 74 had noted fever up to 102 F. and pain in the left side of the chest four days before admission. Three days previously the temperature rose to 103.6 F., and signs at the base of the left lung were detected by his physician, who made a diagnosis of bronchopneumonia and administered penicillin, totaling 400,000 units. His temperature fell to 100.2 F., but on the day of admission the patient became restless, disoriented and confused. He was found to be acutely ill, moaning and unresponsive. His neck was rigid and the Kernig reflex was present bilaterally. A few sticky rales were heard at the base of the left lung. Lumbar puncture yielded a cloudy fluid containing 1,300 cells of which 50 per cent were polymorphonuclear cells. Pneumococci were found on direct smear, which when cultured proved to be type II. The same organisms were recovered from the blood stream. The electrocardiogram showed evidence of hypertrophy of the left ventricle and myocardial damage. Blood pressure was 110 systolic and 80 diastolic. Hemoglobin was 76 per cent; white blood cells numbered 27,000, with 93 per cent polymorphonuclear cells.

He was given an initial dose of 2 Gm. of sulfadiazine intravenously, and 1 Gm. every four hours. Penicillin was given intramuscularly in an intial dose of 100,000 units and in subsequent doses of 25,000 units every three hours. On the morning after admission penicillin was given intrathecally, 100,000 units being injected due to an error, as only 10,000 units had been ordered. In spite of therapy the patient's condition remained unchanged, rigidity of the neck and coma persisting. Fluids and medication were administered through a small caliber (Levin) gastric tube. Thirteen hours after the dose of 100,000 units of penicillin intrathecally, the spinal fluid level was 570 units per cubic centimeter. The spinal fluid culture became negative and remained so for the rest of the hospital stay. Leukocytosis and low grade fever continued. The spinal fluid cell count rose to 13,000 the day after the injection of penicillin and dropped to 2,000 the next day. Three days after the first dose, 10,000 units of penicillin was injected intraspinally, at which time the fluid cells were 180. On the sixth hospital day the cell count was 580. On the seventh hospital day 10,000 units of penicillin was again given intrathecally. Coma and confusion persisted until the tenth day following admission, when the patient began to make steady progress with clearing of the sensorium and diminution of the rigidity of the neck. In a few days the patient had completely regained his faculties. Three weeks following admission the spinal fluid was clear with a cell count of 33. Administration of penicillin intramuscularly and of sulfadiazine by mouth was stopped three weeks after the beginning of therapy. At the time of his discharge, one month after his admission, the patient was asymptomatic and afebrile, although the white blood cell count was still elevated to 13,000 with a normal differential count, and the last lumbar puncture one week before discharge still disclosed 16 cells.

Pneumococcic Endocarditis.—While no cases of pneumococcic endocarditis occurred in this series, one of us (F. D. Z.) has

reported elsewhere 9 cases of acute bacterial endocarditis in the aged of which 3 were due to pneumococci, and 1 was due to a mixed infection by type XI pneumococci and hemolytic streptococci.[30] Thayer[31] and Ruegsegger[32] have directed attention to the occurrence of pneumococcic infections of the heart valves in the higher age groups. Tinsley in a recent review of the subject states, "Pneumococcic endocarditis occurs in about 3 to 3.5 per cent of all pneumococcic infections and is responsible for probably about 5 to 10 per cent of deaths due to pneumococcic infections." In his 16 cases the ages ranged from 27 to 84 years, the average being 50 years. Eleven of the patients were above 45 years of age.[33]

PROGNOSIS AND TREATMENT

Many of the factors governing the prognosis in pneumonia in the aged have already been mentioned, such as the multiplicity and severity of the associated diseases, and the high mortality has been pointed out in cases with apoplectiform onset and with the toxic psychoses, as well as in those in which the disease has an afebrile course or in which cardiac complications develop. In all except 4 of our fatal cases there was multiple lobe involvement. Pneumococcus III infection has always been considered as accompanied with an unusually high mortality rate, especially in the aged. In 65 cases due to pneumococci, there were 16 cases (25 per cent of the total) of type III pneumococcus infection of which only 3 were fatal, but these represented 37.5 per cent of the total deaths in the pneumococcus series. Type III infections, although responding well to modern chemotherapy even in the aged, are nevertheless formidable invaders. Pneumococcus type XX likewise seems to possess high virulence.

The prompt recognition of the existence of a pneumonia and the early use of chemotherapy with appropriate supportive measures constitute the essential factors in treatment of pneumonia in the aged. The drastic lowering of the mortality rate of the group here presented is ample proof of the value of sulfonamide drugs in treatment of pneumonia in the old. That the aged can tolerate them is also well demonstrated. The small series treated with penicillin, 11 cases with no mortality, leads to high hopes for the future, particularly in the cases with preexisting heart disease. In cases without evidence of cardiac damage we make

30. Zeman, F. D., and Siegal, S.: Acute Bacterial Endocarditis in the Aged, Am. Heart J. 29:597-610 (May) 1945.

31. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. 22:1-185, 1926.

32. Ruegsegger, J. M.: Pneumococcic Endocarditis, Arch. Int. Med. 62:388-400 (Sept.) 1938.

33. Tinsley, C. M.: Pneumococcic Endocarditis, Arch. Int. Med. 75:82-88 (Feb.) 1945.

a practice of administering sulfonamide drugs first, switching to penicillin only when no benefit is observed after seventy-two hours, or if the patient cannot tolerate the drug.

In a recent paper on the treatment of pneumococcic pneumonia with penicillin Meads, Harris and Finland [34] have enumerated the general indications for penicillin, and their recommendations are particularly appropriate for aged patients.

Penicillin is the treatment of choice and should be used from the start in the following cases: in patients who are extremely ill and in a shocklike state; in patients with severe cardiac, renal or hepatic damage, particularly if there is edema or azotemia; if there is severe leukopenia; and in patients who are known to be sensitive to sulfonamides and have rashes, fever or severe nausea and vomiting early in the course of treatment with these drugs.

A change to penicillin from sulfonamides is indicated in patients who have received adequate doses and attained adequate blood levels but have failed to respond with improvement in the symptoms and a significant drop in temperature and pulse rate after twenty-four hours or longer, particularly if there is spread of the pulmonary lesion, persistent bacteremia or an increase in the number of pneumococci in the sputum as seen in direct smears; this change is also indicated if leukopenia, delirium tremens, auricular fibrillation or pulmonary edema develops before the symptoms of pneumonia have cleared or if severe untoward reactions. such as acute hemolytic anemia, gross hematuria, oliguria, anuria, nitrogen retention or even drug rash, occur before the pulmonary infection has been controlled. Crystalluria or microscopic hematuria need not be considered a cause for stopping sulfonamides but is an indication for alkalies and for increasing the fluid intake. Penicillin may be used locally when infected pleural fluid or other accessible foci of infection develop, and oral sulfonamides may be continued in such cases.

In the active treatment the patient should be made comfortable in bed, and encouraged to change his position and to move his legs. The question of the proper use of rest in bed is a subject which has again become a matter of active discussion.[35] It is interesting to note how medical opinion has changed with the passage of time. Formerly it was considered unwise to keep old persons in bed because it was believed that this encouraged the development of pulmonary congestion and pneumonia. Today most of the objections to prolonged rest in bed are based on the increased tendency to the formation of peripheral venous thrombi with subsequent pulmonary embolism. We do not feel that rest in bed itself leads to pneumonia in the aged unless the patient is immobilized by a plaster cast or constricting bandages or is unconscious. Phlebitis with the formation of thrombi may be avoided by leg exercises

34. Meads, M.; Harris, H. W., and Finland, M.: Treatment of Pneumococcal Pneumonia with Penicillin, New England J. Med. **232**:747-755 (June 28) 1945.

35. Levine, S. A.: Some Harmful Effects of Recumbency in the Treatment of Heart Disease, J. A. M. A. **126**:80-84 (Sept. 9) 1944; Use and Abuse of Bed Rest, Conferences on Therapy, New York State J. Med. **44**:724-730 (April 1) 1944.

and frequent changes in position. ·We have no fear of keeping old persons in bed until they are well if these precautions are taken. Having established the patient with pneumonia in bed, we see that he is kept as comfortable as possible with attentive nursing care and with the judicious use of sedatives. Codeine and related drugs to control the cough must be given sparingly, since excessive depression of the cough reflex may lead to accumulation of viscid sputum in the smaller bronchi and the development of areas of atelectasis.[36]

The fluid intake is guided in part by the state of the cardiovascular system, but when sulfonamide drugs are given the urinary output should be kept at 1,500 cc. daily. The diet is maintained as·far as possible in accordance with the desires of the patient, but the patient's nutritional status must be evaluated on the basis of history, physical findings and blood studies. Vitamin deficiencies and hypoproteinemia should be sought for and treated actively. Sulfonamide therapy should be started promptly with an initial dose of 4 Gm. given as one dose or fractionally over the course of a few hours, and then maintained at 1 Gm. every four hours throughout the day and night. Each dose of the sulfonamide drugs were used in this manner. The earlier patients bicarbonate. In the series of cases under consideration, all forms of the sulfonamide drugs were used in this manner. The earlier patients in the series were given sulfapyridine and the later ones sulfathiazole or sulfadiazine with the occasional use of sulfamerazine. Sulfadiazine and sulfathiazole were better tolerated than the sulfapyridine and there were few cases in which they had to be stopped because of gastrointestinal symptoms.

Throughout the entire course the blood count and urine must be frequently checked, at least every other day. Blood level determinations are useful in cases in which nonabsorption of the drug is suspected. In only 1 case was it necessary to stop because of renal involvement, and in 1 case because of leukopenia. Dosages in the favorable cases are to be maintained for at least three to four days after the subsidence of temperature and then in smaller doses for the remainder of a week. In none of our fatal cases can it be said that the use of the sulfonamide compounds contributed toward an untoward result. Specific serum was used in 4 cases, in each instance as an adjuvant to chemotherapy. The indication for the use of serum was an extreme toxemia, a positive blood culture or a drug idiosyncrasy, although other severely toxic patients both with and without bacteremia responded to sulfonamide drugs alone. Today there seems to be far less need for serum therapy. Penicillin was

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36. Finland, M., and Loverud, H. I. L.: Massive Atelectatic Collapse of the Lung Complicating Pneumococcus Pneumonia, Ann. Int. Med. **10**:1828-1847 (June) 1937.

administered intramuscularly in doses of 15,000 to 20,000 units every three hours.

The importance of combining specific therapy with carefully planned supportive therapy has been stressed by Armstrong, England, Favour and Scheinberg,[37] who point out that one may expect to see new clinical pictures in connection with pneumonia, as specific and bacterial agents permit prolonged survival in the face of infections otherwise rapidly fatal. One of their 2 examples is an 85 year old man who had previously been undernourished and who had pneumonia following a suprapubic prostatectomy. The pulmonary infection was slowly brought under control with sulfonamide drugs and penicillin. This drug also served by intrapleural injection to clear up an effusion in the right pleura. The real problem had to do with the patient's impaired *nutrition as indicated by the reduction of the plasma proteins to 3.3 Gm.* per hundred cubic centimeters. This was further aggravated by nausea, vomiting and diarrhea. In addition a severe anemia was found, the red cells at the low point being 2,900.000 per cubic millimeter and the hemoglobin 8.2 Gm. per hundred cubic centimeters. To combat the hypoproteinemia and the anemia whole blood was given in six transfusions to the total of 2,900 cc.; plasma was given fifteen times, totaling 4,550 cc., and amino acids were administered by mouth to the amount of 3,330 cc. As a result of this truly heroic treatment the patient recovered.

The use of oxygen inhalation is a valuable adjuvant, especially when pulmonary absorption has been impaired by associated cardiovascular or respiratory disease. The administration by oxygen mask seems to be the preferable method, as it is well tolerated by the aged person and does not interfere with nursing care. Recent studies emphasize the need for starting oxygen therapy before the anoxia becomes obvious.

The treatment of the associated diseases is equal in importance to the specific therapy of the pneumonia. Diabetes must be controlled with insulin and dietary measures. Digitalis, although not a routine measure, must be employed in those cases in which there is auricular fibrillation or obvious congestive heart failure, or which present early signs of cardiac insufficiency. Mercurial diuretics may be employed to advantage when frank congestive failure is present. By combining active treatment of the failing heart with use of the antibacterial drugs one may expect even greater reduction in mortality.

37. Armstrong, S. H., Jr.; England, A. C.; Favour, C. B., and Scheinberg, I. H.: Anemia and Hypoproteinemia Complicating Severe Protracted Pneumonia, J. A. M. A. **127**:303-306 (Feb. 10) 1945.

CLASSIFICATION OF PULMONARY INFECTIONS

Since the series of cases which has been presented is relatively small and fails to give the whole picture of pulmonary infections seen in the higher age groups, the complete classification presented in table 4 will aid in analyzing the varieties of pneumonia occurring in the aged. A few brief explanatory comments will suffice on the types of pneumonia occurring in the aged which have not already been discussed. Mycobacterium tuberculosis as a cause of pneumonia in the aged must never be forgotten, and the organisms must be searched for in the sputums of all patients with persistent signs referable to the lungs, or whose illness resists specific therapy. Roentgenologic examination may be misleading. Pasteurella tularensis as the causative agent in the pneumonia of old age is mentioned here for the sake of completeness.[38] Ornithosis, the recently recommended designation for psittacosis and related conditions,

TABLE 4.—*Classification*

A. Pneumonia due to specific organisms
    1. Diplococcus pneumoniae
    2. Streptococcus pyogenes
    3. Staphylococcus aureus
    4. Klebsiella pneumoniae
    5. Mycobacterium tuberculosis
    6. Pasteurella tularensis
B. Pneumonia due to filtrable viruses
    1. Ornithosis
    2. Primary atypical pneumonia ("virus pneumonia")
    3. The pneumonia of epidemic influenza
C. Suppurative bronchopneumonia (Neuhof)
D. Pneumonia of undetermined bacteriologic origin
E. Aspiration pneumonia
    1. Chronic lipid pneumonia
    2. Pneumonia following aspiration of stomach contents
    3. Foreign bodies in the bronchi
F. Postoperative pneumonia
    1. Associated with antecedent infection of the upper respiratory tract
    2. Associated with chronic cardiovascular or pulmonary disease
    3. Associated with lobar or lobular atelectasis due to:
        a. too profound anesthesia
        b. too much sedative medication
        c. shock and hemorrhage
        d. constricting bandages or plaster casts

is caused by a virus transmitted by parrots, canaries, pigeons, chickens and other birds. There are many similarities between this type of pulmonary inflammation and that which is now termed "primary atypical or virus pneumonia." One opinion, as expressed by Favour,[39] is that the virus is the same and has become fixed in man and incapable of heterogeneous parasitism. The experience of the Commission on Acute Respiratory Diseases of the United States Army is directly opposed to this view. Dingle [40] states that the great majority of cases of primary

38. Stuart, B. M., and Pullen, K. L.: Tularemic Pneumonia: Review of American Literature and Report of Fifteen Additional Cases, Am. J. M. Sc. **210**: 223-236 (Aug.) 1945.

39. Favour, C. B.: Ornithosis (Psittacosis), Am. J. M. Sc. **205**:162-187 (Feb.) 1943.

40. Dingle, J., and others: The Present Status of the Etiology of Primary Atypical Pneumonia, Bull. New York Acad. Med. **21**:235-262 (May) 1945.

atypical pneumonia observed in army hospitals is not caused by psittacosis or related viruses.   In the commission's three years of experience the diagnosis of psittacosis or ornithosis has not once been established in a series of more than 500 cases of atypical pneumonia and related respiratory infections.

The chronic lipid pneumonias are thought to be more prevalent than is generally realized, especially in the aged.   The administration of medication in oily sprays and nasal drops is responsible for large collections of oil with surrounding fibrosis in the bronchopulmonary tree, which may later become infected.[41]   The aspiration of stomach contents into the trachea and bronchi with a subsequent pneumonia may occur postoperatively, either while the patient is still under the influence of the anesthesia or as the result of regurgitation from a dilated stomach or during unconsciousness from any cause such as a cerebral injury, a cerebral accident or attempts at suicide with hypnotic drugs.[42]   The postoperative pneumonias are mentioned here because of the increasing number of operations performed on aged persons.   The problems presented by these cases deserve special consideration, and for this reason no cases have been included in our present series, although some of the important features are enumerated in table 4.

These groups are not always clearcut and may actually overlap. The organism identified by methods of sputum culture may at times be only an incidental finding, whereas in cases classified as having the bacterial origin undetermined, it may be that either no attempt was made to identify an organism or that it was impossible to obtain material for identification.   Too frequently this is true in cases involving the aged, in which the pneumonia may have been overlooked, or the patient may not have cooperated, or the patient may have died before additional specimens of sputum could be obtained.

SUMMARY

One hundred and sixty-six cases of pneumonia in men and women 60 years of age and older have been studied.   Of these, 33 cases, or 20 per cent, were fatal.   Included in the series are 65 cases due to various types of pneumococci, of which 8 terminated fatally, or 12 per cent.   Sulfonamide therapy was used in 128 cases.   Additional type-

41. Bishop, P. G. C.: Oil Aspiration Pneumonia and Pneumolipoidosis, Ann. Int. Med. **13**:1327-1359 (Feb.) 1940. Freiman, D. G.; Engelberg, H., and Merritt, W. H.: Oil Aspiration (Lipoid) Pneumonia in Adults, Arch. Int. Med. **66**:11-38 (July) 1940. Cannon, P. R.: The Problems of Lipid Pneumonia, J. A. M. A. **115**:2176-2179 (Dec. 21) 1940.

42. Irons, E. E., and Apfelbach, C. W.: Aspiration Bronchopneumonia, with Special Reference to Aspiration of Stomach Content, J. A. M. A. **115**:584-587 (Aug. 24) 1940.

specific serum was given in 5 of these cases. Penicillin was used successfully in 11 cases, including an empyema due to type III pneumococci in a man aged 84 years and a meningitis due to type II pneumococci in a man aged 74 years.

Although the mortality has been dramatically reduced by recent advances in therapy, pneumonia is still a disease with high incidence and high mortality in the aged. With the proper appreciation of the complex problems encountered in the old, and with better methods of treatment, one may look for further improvement in the results. The disease appears in unusual forms both in its onset and in its course in the aged, and is commonly associated with other conditions which may obscure and aggravate it. Physicians should be on the alert for pneumonia in the aged, recognize it when it is present and treat it actively in spite of what may appear to be overwhelming obstacles. Its occurrence should not be assumed merely because of its prevalence in the aged or because of the presence of a few rales at the bases of the lungs. The period of medical development is past when an unqualified diagnosis of pneumonia on the death certificate of an elderly person was considered adequate because no one expected old persons to recover from the disease.

Progress in Internal Medicine

ALLERGY

A Review of the Literature of 1944 and 1945, with Comments on Future Problems

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DURING the war there has been little opportunity for careful study of such a chronic disease as allergy. With a few exceptions the medical officers in the Army have been unable to accomplish much beyond the clinical classification of their patients, and in civilian life the pressure of routine work has precluded comprehensive or thoughtful studies. Now, however, the war is over, our young physicians are coming back slowly but surely and one can expect that before long opportunities for intensive full time work in the form of residencies and fellowships in allergy will become available and so make further progress possible. In a recent number of the *Atlantic Monthly*, Prof. Harlow Shapley [1] has written a striking paper. After describing the "advantages" of war—the full employment, the large wages, the increase in circulating currency and, above all, the unity of purpose and action—he pointed to what might happen if this same unity of purpose could be applied to the advancement of science. If cooperation could be fully established, even a small fraction of the effort and the expense of war applied to peace might result in extraordinary benefit to everybody. Professor Shapley suggested that if every scientific investigator would write down the questions which he needs to have answered in his own research it might easily happen that one of his fellows, even though working in a different field, might know the answer or at least give him a suggestion which would help him promptly and effectively. It is the unity of purpose which is so important.

The recent literature on allergy is not impressive either in volume or in content, but in reviewing it I shall try to point to some of the questions which trouble me.

In the allergy clinic, one sees a variety of symptoms. There are hay fever, asthma in young people and eczema in each of which the histories usually show a clear relation between the symptoms and the changes in environment or diet. The positive reactions to skin tests observed are anticipated, and they confirm the diagnosis. For these

1. Shapley, H.: A Design for Fighting, Atlantic Monthly **176**:107, 1945.

conditions allergy by itself appears to be an adequate explanation. But there are other cases, in which the diagnosis is not so easy. There is chronic rhinorrhea called vasomotor rhinitis, there is asthma beginning after a person has reached the age of 40, there are cutaneous lesions not readily explained and there is migraine headache. In addition, in the patient with severe asthma complications develop: Polypoid sinusitis is common. Periarteritis nodosa and Loeffler's syndrome are not so common. Peptic ulcer and gastric hemorrhage have been seen. Then, more recently, from the Pacific have come a few patients with "tropical eosinophilia."

All these patients are grouped together chiefly because their symptoms are so similar; they are also grouped together because any and all combinations of these symptoms occur either together or in sequence and finally because inheritance of the "asthmatic state" seems to establish the "allergic person" as one who is more likely than his fellows to have one or another of the symptoms listed develop. The term "asthmatic state" has in this sense a broader meaning than the term "allergy." It is the background on which allergy may develop. Also it is the background from which asthma from other causes beside allergy may come. It indicates a reaction pattern which is characteristic. Let it be called x.

A patient who has x and who has eczema in infancy will be more likely than others to have hay fever and asthma develop later. He is not nearly so likely to have arthritis or gastrointestinal disturbances develop. Why stop to consider an x for asthma and allergy when another philosopher might suggest a y for arthritis or a z for mucous colitis? Is the group of patients with "allergic" manifestations any more characteristic than the group with arthritis? I think so, chiefly because of the evidence that the asthmatic state is a disturbance which not only is generalized but runs true to its form. In passing, one can observe that for each person the reaction pattern appears to be uniform and fairly constant. Hay fever, asthma and eczema—each symptom tends to recur in the individual patient, and the fact suggests a local change in the tissue rather than a generalized change. However, when the primary process increases in severity and goes "out of control," then other manifestations in the same symptom group may be added to the picture. Severe hay fever leads into asthma and sometimes to urticaria as well. Combinations of eczema and asthma are found, and the combination of chronic vasomotor rhinitis and asthma with thick membrane in the sinuses is typical enough.

It is the multiplicity of typical symptoms occurring together or at different times in the same patient which forces the conception of a generalized disease entity. In the allergic patients the positive reactions to skin tests and the antibodies (reagins) in the blood serum confirm

the theory, and then, finally, when the person marries his children are more likely than others to have manifestations of allergy develop. The evidence of a "constitutional" change is ample. More studies of the natural history of the allergic patient will throw a sharper light on the process. Clein [2] has made a ten year study of 100 allergic children, but 100 children are not enough and ten years are not enough. The histories of many patients in whom asthma has developed in their thirties and forties show that they, too, had eczema in infancy. How often does this infantile eczema subside in two or three years to leave the child perfectly normal for the rest of his life, and, on the other hand, how often is this early symptom of allergy followed later by the development of other manifestations? Is there any characteristic of the early disease which would throw light on the ultimate prognosis? As Clein points out, eczema is the first symptom in early childhood, but rhinitis and hay fever are the important symptoms later on. Whereas the symptoms of allergy change from time to time, the fundamental allergic state continues, and so it is that these persons are the ones in whom asthma develops later in life; perhaps also they are the ones in whom reactions to the sulfonamide drugs or penicillin develop or who show such alarming symptoms as were described by Sprague and Barnard [3] in a soldier who reacted violently to yellow fever virus because he had retained his sensitiveness to egg. Presumably patients in whom asthma develops for the first time after they have reached the age of 40 also have x, and presumably patients with primary organic emphysema do not have x. It will take many statistical studies to make sure about these things. The point of this argument is that further knowledge of the asthmatic state should reveal the basic nature of the disease and so lead to a new approach to its treatment. So far the best one can do is to say that it is inherited.

The immediate cause of each symptom is a physical change in the local tissues. The lesions and the symptoms which they produce are listed in the table. One observes that these lesions are reversible and that one can ascribe each of them to a disturbance which is "vasomotor" in the broad sense. Each of the symptoms occurs in attacks.

The exciting cause of the local disturbance has been considered to be histamine or at least H substance, but then comes the question: Is the trouble due to excessive release of histamine, or is it due to excessive reaction to the normal quantity? What starts the process?

2. Clein, N. W.: The Growth and Development of Allergy: A Ten Year Study of One Hundred Allergic Children from Birth to Ten Years of Age, Ann. Allergy **1**:3, 1945.

3. Sprague, H. B., and Barnard, J. H.: Egg Allergy, U. S. Nav. M. Bull. **45**:71, 1945; abstracted, J. A. M. A. **129**:578 (Oct. 20) 1945.

Allergy can do it, but evidently there are other mechanisms as well. As will be described later, there is depletion in both the somatic and the psychic sense; there is infection, and there is intoxication by drugs. Each of these factors can cause asthma, but whether the action is in each case produced by the release of H substance remains to be demon-

Lesions of Allergy and the Symptoms Which They Produce

Lesions	Symptoms
Vasodilatation	Eczema, erythema (migraine ?)
Vasoconstriction	Eczema (migraine ?)
Smooth muscle spasm	Asthma, colic
Increased activity of the glands	Asthma, hay fever, hydrorrhea due to vaso-motor neurosis
Increased permeability of the capillaries	Hay fever, urticaria
Narrowing of the blood vessels	Periarteritis nodosa, purpura
Hemorrhages of the mucous membrane	Peptic ulcer
Hypoplasia of the bone marrow	Agranulocytosis, purpura, anemia
Shifts in blood cell counts	Eosinophilia
Lesions of the joints (?)	Arthritis ?

strated. The relationship between these factors can be summarized in a diagram (see the chart).

In general one can postulate for the development of "allergic symptoms" the following requirements: (*a*) a person with a certain inheritance (asthmatic state) has (*b*) the capacity to develop sensitiveness

Diagram of relationships in the production of "asthmatic" symptoms.

(allergy) and also (*c*) the capacity to produce and/or to react to H substance so as to cause (*d*) a variety of symptoms of vasomotor origin.

Each of these topics can now be considered in some detail, but, first of all, how common is the asthmatic state?

The incidence of the asthmatic state is hard to define in precise figures. Hyde and Kingsley [4] rejected for allergy only 495 out of 60,000 draft registrants—less than 1 per cent. One can hope that later on the medical history of the war will produce still other figures like this. Among the diseases of the total patients admitted to any military hospital, allergy ranks high. In several areas asthma ranks third among the disabling diseases. Psychic and gastrointestinal disorders come first and second respectively. At the Percy Jones General Hospital, Alford [5] found that asthmatic patients constituted 10 per cent of all persons admitted. Colonel French,[6] who has been so enthusiastic and persistent with the organization of allergy clinics in the Fourth Service Command, reported 9,591 patients with asthma, 5,373 with hay fever, 3,831 with perennial allergic rhinitis and over 4,000 with miscellaneous diseases from a total number of 32,000 patients examined in the fifty clinics under his direction. As outlined in a previous review,[7] patients who received discharges from military service because of asthma vary from 3 to 6 per cent of those admitted to the hospital. It is obvious that the problem of allergy is large.

The asthmatic state—the x—concerns allergy in particular, but, as the diagram shows, the same symptoms may arise from other exciting causes. Depletion is one, and it has two parts: somatic and psychic. There are patients in whom poor health in general, with loss of weight and strength, appears to be sufficient cause for the asthma or the chronic rhinitis or the urticaria or the eczema; at least the improvement which comes from appropriate treatment on a general basis and without regard to allergy is striking. It is interesting to consider that they too have x and that this explains why they have one or another of the asthmatic symptoms. They may have abscessed teeth, chronic diseases of the gallbladder or prostate or other evidences of chronic infection. Chronic infectious sinusitis belongs in the category but deserves special considerations because its treatment is so uncertain and hazardous. In many if not most of the cases, the lesions in the sinuses appear to be the result and not the cause of the process. More interesting are the cases of psychic origin. It is better to say that they result from stress and strain. Except for the presenting symptom, the asthma or the eczema perhaps, and the depletion, physical

4. Hyde, R. W., and Kingsley, L. V.: Distribution of Allergic States in Selectees, J. Allergy **14**:386, 1943.

5. Alford, R. I.: The Distribution of Patients with Bronchial Asthma: First Hundred Cases of Bronchial Asthma Admitted to the Percy Jones General Hospital, J. Allergy **25**:196, 1944.

6. French, S. W., and Halpin, L. J.: Army Allergy: Fourth Service Command 1943, Ann. Allergy **2**:365, 1944.

7. Rackemann, F. M.: Allergy: A Review of the Literature of 1943, Arch. Int. Med. **73**:248 (March) 1944.

examination is noncontributory. There is no evidence of allergy. There are several theories to explain this depleted group.

THE ENDOCRINE THEORY TO EXPLAIN DEPLETION

Outwardly and on physical examination, the patients appear normal. Certainly, there is no evidence to suggest hyperthyroidism or hypothyroidism or the excess or the deficiency of any other endocrine gland in the group as a whole. More recently, Harkavy [8] pointed out that in animals anaphylaxis may be inhibited by removal of the thyroid, the parathyroid, the thymus or the testes whereas anaphylaxis may be enhanced by removal of the ovaries, the adrenals or the hypophysis. In human beings, on the other hand, these artificial changes make no difference to the allergy. *The cellular reactions are not initiated by the endocrine or the autonomic nervous system.* Zondek and Bromberg,[9] in Palestine, made skin tests with various endogenous hormones—estradiol, estrone, progesterone, testosterone and others. In a group of 27 allergic persons they found positive reactions in 19 (70 per cent), whereas similar tests on 32 normal persons elicited no reactions at all. However, 19 patients with pruritus vulvae and acne reacted like the allergic persons in 72 per cent of the cases. There is little so far to support any endocrine theory. Albright [10] objected strenuously to the belief "that anything which is not understood belongs to endocrinology," and I agree. On the other hand, the next section, on the alarm reaction, considers the role of the adrenal, and that is endocrinology.

THE ALARM REACTION

The conception of Selye [11] that the body reacts to stimuli of all sorts in a pattern which is more or less uniform, at least in the qualitative sense, and that this reaction pattern depends on the activity of the adrenal cortex is of considerable interest and may be pertinent to our subject. Selye explained that the first effect of injury is to produce the alarm reaction, the symptoms of which are recognized as varying degrees of surgical shock. The first stage is brief. After it the resis-

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8. Harkavy, J.: The Influence of Neuro-Hormonal Regulations on Anaphylaxis and Allergy, J. Mt. Sinai Hosp. **0**:565, 1944.

9. Zondek, B., and Bromberg, Y. M.: Endocrine Allergy, J. Allergy **16**:1, 1945.

10. Albright, F.: Introduction to Diseases of the Ductless Glands, in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1943, p. 1203.

11. Selye, H.: The Alarm Reaction, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery and Specialty, ed. 2, Philadelphia, F. A. Davis Company, 1940. Selye, H., and Pentz, E. I.: Pathogenetical Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. **49**:264, 1943. Selye, H.; Sylvester, O.: Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, J. A. M. A. **124**:201 (June 22) 1944.

tance rises so that further stimulation of the same sort will no longer produce the same effect. The patient is in the stage of countershock. During the resistant, or countershock stage the symptoms and signs, if any, are those of adrenocortical overdosage, and this if long continued will lead to a variety of lesions, some of which can be recognized in cases ·of advanced asthma. The pathologic picture called periarteritis nodosa is one. Lesions in the joints with infiltrations of lymphocytes and the production of granulomatous areas is another. A number of separate hormones have been isolated from the adrenal cortex. Desoxycorticosterone is one of these, and when rats are treated by injections of this substance many interesting changes occur. The thymus and the pancreas degenerate, and there may be ulcerations of the gastrointestinal tract; the lungs become hyperemic. Meantime, the temperature falls and the rate of basal metabolism falls, but the blood sugar and the nonprotein nitrogen levels increase. There is dehydration with concentration of the blood, so that the white cell count and the red cell count go up. These effects—and the list here is only partial—are produced in animals under artificial conditions. In the clinic one sees such symptoms as periarteritis nodosa in occasional cases of severe asthma. I recall at least 2 patients with severe asthma in whom a gastric hemorrhage developed from a peptic ulcer. Whereas it is not often possible to recognize the symptoms of the resistant stage of Selye in a patient whose asthma is not severe, nevertheless the whole conception is pertinent to the problem of asthma, and it may well be that when more is known about the functions of the adrenal cortex one can recognize that asthma occurs because of some disturbance of the adrenal mechanism.

Meantime, Albright,[12] in a fascinating lecture on Cushing's syndrome, has presented the theory that during the resistant, or countershock, stage the sugar-regulating mechanism of the adrenal gland (he calls it the S hormone) is produced in great excess, thereby depleting the body, whereas the nitrogen-building factor (the N hormone) is withheld during the stage of countershock. This means that the tissue is broken down at a rapid rate and without attempt at repair.

A patient with severe asthma, a tired business man of 50 years, was seen last year by Dr. Albright in consultation.[13] The man was greatly depleted in body weight and strength. His asthma was severe. The fact that he excreted only 5 mg. of 17-keto steroids in place of a normal excretion of about 15 mg. was taken as evidence that his nitrogen-building adrenal hormone was deficient. He was considered to be in

12. Albright, F.: Cushing's Syndrome, in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press, 1943, vol. 38, p. 123.

13. Rackemann, F. M.: Medical Progress: New Theories Concerning Asthma, New England J. Med. **230**:284, 1944.

the countershock stage of the alarm reaction, and his severe asthma was considered as a part of that process. Aside from rest in bed and general care of the best sort this man was given injections of testosterone proprionate, and he did well. At the same time, however, patients with a somewhat similar picture had likewise done well simply on the rest in bed and good nursing care, without the extra hormonal treatment. Last winter I [14] described depletion as an important factor in severe asthma and, in doing so, implied that the patient was in the countershock stage of the alarm reaction and that the cause of his trouble was concerned in some way with adrenal disturbances. Meantime, of course, there are patients who have been treated with an adrenal cortex extract (Eschatin) and other commercial preparations of adrenal cortex hormones without success. The theory has been considered before, but it must be considered again. It has opened an immense field for further investigation.

One must recognize, however, that this theory about the alarm reaction and the effect of adrenal hormones is concerned probably more with the effects of the allergic reaction than with the cause, of it. The reaction is a response to stimuli, and the allergy produces the stimulus. It is considered here because it may offer a possible explanation for the fact that allergy develops only in certain persons. Perhaps it is that in their cases the symptoms and signs of the alarm reaction develop more promptly and from slighter causes than happens in the cases of normal persons.

Chronic vitamin deficiency must be considered as a cause of depletion. Do the signs and symptoms of asthma or the appearance of allergy per se appear at a certain time because the person is in poor condition because of improper feeding? Vitamin A has been discussed by Clausen,[15] who pointed out that patients with chronic infections are apt to have low levels of plasma vitamin A and that their resistance to infection falls when the vitamin A is depleted. Ascorbic acid is concerned with the production of antibodies. It was thought at one time that large doses of ascorbic acid might do good in hay fever and asthma, but Friedlaender and Feinberg [16] have studied the question, finding that the blood level of vitamin C is normal in hay fever and that treatment with as much as 500 mg. of ascorbic acid daily did *no good*. Hebald [17] agreed. There is no evidence that ascorbic acid plays any

14. Rackemann, F. M.: Depletion in Asthma, J. Allergy **16**:136, 1945.

15. Clausen, S. W.: Absorption of Vitamin A and Its Storage in Tissues, in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press, 1943, vol. 38, p. 199.

16. Friedlaender, S., and Feinberg, S. M.: Vitamin C in Hay Fever: Therapy and Blood Levels, J. Allergy **16**:140, 1945.

17. Hebald, S.: Clinical Evaluation of Ascorbic Acid in the Treatment of Hay Fever, J. Allergy **15**:236, 1944.

part in the disease. Incidentally, Rocha e Silva [18] gave large doses (200 to 500 mg.) of ascorbic acid to rabbits before testing for anaphylactic shock and found that the treated animals were no different from the controls; the ascorbic acid had no effect either on the intensity of the shock or on the reduction of the histamine content of the blood after it.

Psychic disturbances can cause queer symptoms. There are occasional cases of asthma in which they are so important as to constitute a rational explanation for all the trouble. Some interesting figures may be quoted here. As said before, Hyde and Kingsley [4] rejected about 1 per cent of draftees on account of asthma and other allergic disorders. In a group of 11,647 patients afflicted with functional psychoses, Leavitt [19] found only 10 patients with asthma, and in another group of 5,000 mentally defective and epileptic persons not one patient with asthma was observed. Dr. Stanley Cobb [20] agreed with Leavitt that the incidence of certain chronic disorders like arthritis and asthma are rare among insane persons, and he explained it this way: When a person becomes anxious and frustrated so that he loses control of his emotions, one of three things, and only one, may happen. First, he may regain control and recover; second, his loss of control may go on to complete psychic deterioration, or, third, his emotional tension may spill over into the development of somatic symptoms, usually of the vasomotor group of disturbances, notably, asthma, urticaria, eczema or arthritis, any one of which can provide an outlet for his emotional suffering. These three directions are quite distinct one from the other. In a patient who goes on to psychic deterioration, vasomotor symptoms do not also develop: insane patients do not have vasomotor disturbances, and they do not have asthma. In the meantime, Zeller and Edem [21] made skin tests by the scratch method with pollen on 372 patients in a hospital for insane persons and found positive reactions in 15, or 4 per cent, and all but 1 of these had clinical hay fever. Allergy was present in a normal proportion, and the symptoms due direct to the allergy developed as usual. It was the extra symptoms, built up on a psychic basis, which were lacking in the insane persons.

This discussion suggests, therefore, that in persons who have inherited the asthmatic state depletion, whether of the soma or of the psyche, may result in asthma or, for that matter, in any other manifestation of the state, such as chronic urticaria or eczema or polypoid sinusitis.

18. Rocha e Silva, M.: Failure of Ascorbic Acid to Influence the Variations of the Histamine Content of Rabbits Blood During Anaphylactic Shock, Rev. brasil. de biol. **3**:39-44, 1943.

19. Leavitt, H. C.: Bronchial Asthma in the Functional Psychoses, Psychosom. Med. **5**:39, 1943.

20. Cobb, S. S.: Personal communication to the author.

21. Zeller, M., and Edem, J. V.: Allergy in the Insane, J. Allergy **14**:564, 1943.

The observations of Selye [11] and Albright [12] suggest that one of the factors in this depletion is a disturbance of the adrenal cortex, but much more information is needed. Here, indeed, is a problem for further study.

What about infections and intoxications? In these two categories there is always the question of selective localization dependent on the function of the bacteria or the drug, but more reasonable is another aspect of allergy. In certain patients sinusitis develops with regularity with each new head cold; other patients will have bronchitis: I have seen chronic atopic eczema flare up with infections, and I have seen urticaria develop in a day or two after a new head cold. One must consider that certain tissues are more susceptible to the bacterial toxin and that this may depend on a specific reaction factor—an antibody—and that means allergy. Here again the reaction pattern remains true to form; the "asthmatic state" is still important.

THE LESION IN ALLERGY

The basic lesion in allergy consists in the capacity to develop sensitiveness. That is the difference between persons who are allergic and those who are normal. · Meantime, the allergic reaction with swelling and edema, with the dilatation of small capillaries and the constriction of entering arteries, has been discussed as protective in nature—the purpose being to hold the offending substance at the site of entrance and so prevent it from invading the body. How about the absorption of foreign substances from the gastrointestinal tract of sensitive and nonsensitive persons? Can the protective effect of allergy be demonstrated in this way? Is there any evidence that absorption of the specific substance is inhibited in persons who are sensitive to it? The question has been studied by Hecht and others [22] in Sulzberger's clinic, and with interesting results. The skin of normal persons was sensitized with the serum of a patient highly sensitive to ragweed pollen, and then two days later the person was given, on a fasting stomach, capsules containing 5 Gm. of ragweed pollen. Sixteen of the 22 subjects absorbed enough ragweed to cause a reaction in the passively sensitized skin site. However, the reactions varied, and it was found later that the absorption was influenced by the presence of acid or alkali in the stomach. The administration of acid tended to prevent the absorption, whereas the administration of alkali tended to increase it. The results of this experiment are interesting; the method used is also interesting because it shows how the absorption of foreign protein substances might be studied fairly easily. The results are comparable

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22. Hecht, R.; Mosko, M. M.; Lubin, J.; Sulzberger, M. B., and Baer, R. L.: The Absorption of Whole Ragweed Pollen from the Gastro-Intestinal Tract, J. Allergy **5**:9, 1944.

to those obtained previously by Walzer and Golan,[23] who have made extensive studies on the absorption of foreign substances which were administered in considerable variety and by different methods. One would suppose that this general technic ought to be of considerable interest to students of digestion and nutrition.

HISTAMINE

The chart presents the theory that the asthmatic state sets the stage so that the actor will respond with various vasomotor symptoms when prompted in various ways. Allergy is the first and typical way, but depletion, infection and intoxication appear to be other ways if clinical observations can be trusted. The stage plus the prompting makes the patient release H substance. Is this diagram correct? Does the action in each case involve H substance? Does depletion, for example, cause asthma or vasomotor rhinitis because it liberates histamine or changes the reaction toward it? Could H substance have anything to do with Loeffler's syndrome?

First, let me review the points about histamine which are pertinent to this discussion. It was in 1910 that Barger and Dale[24] isolated β-imidazolylethylamine (histamine) from ergot and in 1911 that Barger and Dale[25] found histamine in the intestinal mucosa. Since then its precursor, histidine, has been recognized as a common constituent of body cells. As Best and McHenry[26] stated, it is found especially in all the barrier tissues—the skin and the intestinal mucosa. In 1927, Best, Dale, Dudley and Thorpe[27] showed that the mother substance, histidine, was available in ample quantities and that the antigen-antibody reaction of allergy was capable of removing the carboxyl group to change histidine into histamine in the living animal. Bacterial action also can cause this change.

In a comprehensive review before the American Academy of Allergy in 1944, Dragstedt[28] declared that the release of histamine is at least a major factor in the production of allergic symptoms in man although it is not necessarily the only factor involved. The fact is that whereas

23. Walzer, M.: Absorption of Allergens, J. Allergy **13**:554, 1942. Walzer, A., and Golan, H. G.: The Transport of Antigen Through the Body by Electrophoresis, ibid. **16**:165, 1945.

24. Barger, G., and Dale, H. H.: The Presence in Ergot and Physiological Activity of B-Imidazolethylamine, J. Physiol. **40**:38, 1910.

25. Barger, G., and Dale, H. H.: B-Iminazolylethylamine: A Depressor Constituent of Intestinal Mucosa, J. Physiol. **41**:499, 1911.

26. Best, C. H., and McHenry, E. W.: Histamine, Physiol. Rev. **11**:371, 1931.

27. Best, C. H.; Dale, H. H.; Dudley, H. W., and Thorpe, W. V.: Nature of Vaso-Dilator Constituents of Certain Tissue Extracts, J. Physiol. **62**:397, 1927.

28. Dragstedt, C. A.: The Significance of Histamine in Anaphylaxis and Allergy, Quart. Bull. Northwestern Univ. M. School **17**:102, 1943.

histamine has been isolated from many tissues and identified as such it has not been "caught red handed at the scene of the crime." Sir Thomas Lewis [29] recognized this when he made the first reference to H substance. He wrote, "I shall speak of an 'H.-substance' and in using it shall mean any substance (or substances) that is liberated by the tissue cells and exerts in the minute vessels and nerve endings an influence culminating in the Triple Response."

When most authors discuss histamine what they refer to is the property of the experimental extracts—blood serum, tissue fluid or cell suspension—to produce a characteristic contraction of guinea pig muscle or to produce a fall in the peripheral blood pressure of the cat. To exclude depressor substances other than histamine the experimental fluid must be acidified and boiled, and under these conditions it is most probable that the reactions produced do depend in fact on histamine.

The development of the knowledge of histamine by a long series of experiments has been summarized recently in an excellent review by Code.[30] Recent advances concerning the histamine problem have been described by M. Rocha e Silva.[31] In the blood of animals, Code [32] himself showed that the white cells contained a large amount of histamine while the plasma had little. Later, Code and Ing [33] extracted the active principle from the white cell layer of rabbit blood and identified it as histamine. In the rabbit and under the conditions of that experiment, H substance really was histamine. Leukopenic blood contains less histamine in accordance with the diminished white cell count.

In anaphylactic shock in both guinea pigs and dogs the amount of histamine-like activity in the blood will rise, but, as Code [34] found, this rise is transient and in a few minutes the concentration falls to normal. More important for the theory here are the many experiments which show that histamine-like activity is released from the tissues of animals during the anaphylactic reaction. Katz [35] found that when a solution

29. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

30. Code, C. F.: The Mechanism of Anaphylactic and Allergic Reactions: An Evaluation of the Role of Histamine in Their Production, Ann. Allergy 2:457, 1944.

31. Rocha e Silva, M.: Recent Advances Concerning the Histamine Problem, J. Allergy 15:399, 1944.

32. Code, C. F.: The Source in Blood of the Histamine-Like Constituent, J. Physiol. 90:349, 1937; The Histamine-Like Activity of White Blood Cells, ibid. 90:485, 1937.

33. Code, C. F., and Ing, H. R.: Isolation of Histamine from White Cell Layer of Centrifuged Rabbit Blood, J. Physiol. 90:501, 1937.

34. Code, C. F.: The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock, J. Physiol. 127:78, 1930.

35. Katz, G.: Histamine Release from Blood Cells in Anaphylaxis in Vitro, Science 91:221, 1940.

of egg white was added to the blood cells of a rabbit sensitized to egg and the mixture was incubated the plasma contained from two to six times as much histamine as did the plasma of the same blood before treatment. Incidentally, he commented on this observation as an indication of a method of study which might be useful in clinical allergy. In the next year Katz and Cohen [36] studied patients with ragweed hay fever and found that the method worked.

When the organs of sensitized animals are removed and then perfused with salt solution to which a quantity of antigen is added, histamine-like activity can be demonstrated in the perfusate. This was found first in 1932 by Bartosch, Feldberg and Nagel.[37] Schild [38] observed that the perfusate from lungs treated with antigen contained histamine activity but that the perfusate from lungs treated with barium chloride, which also caused contraction of the bronchial muscles, did not show it. The histamine activity did not come from the muscle spasm alone. Since then, histamine-like activity has been found by various workers in other organs perfused during and after anaphylaxis. Dragstedt and Mead [39] found it in the lymph of dogs in anaphylactic shock. Meantime, Dragstedt [28] noted that the identification of histamine itself in the blood is always difficult because the quantities are so small. He calculated that a dog weighing 10 Kg. has only 0.75 mg. of histamine in his entire blood stream.

In patients with allergy, Rose [40] has shown that the concentration of blood histamine changes during attacks of asthma and of urticaria. During the first minutes there is in human beings, as in animals, an increase in blood histamine, and later there is a fall. One should note, however, that the relation between the amount of histamine activity in the blood and the symptoms is not so direct as one would like to expect. Whether the discrepancy depends on technic, including the time when the samples were taken, or whether it shows that some other factor is operating at the same time is debatable.

In his evaluation, Code [30] pointed out that there is evidence to suggest that along with histamine other substances, notably heparin, may

36. Katz, G., and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, J. A. M. A. **117**:1782 (Nov. 22) 1941.

37. Bartosch, R.; Feldberg, W., and Nagel, E.: Das Freiwerden Eines Histaminähnlichen Stoffes bei der Anaphylaxie des Meerschweinehens, Arch. f. d. ges. Physiol. **230**:129, 1932.

38. Schild, H.: Histamine Release and Anaphylactic Shock in Isolated Lungs of Guinea Pigs, Quart. J. Exper. Physiol. **26**:165, 1936.

39. Dragstedt, C. A., and Mead, F. B.: Role of Histamine in Canine Anaphylactic Shock, J. Pharmacol. & Exper. Therap. **57**:419, 1936.

40. Rose, B.: The Relation of Histamine to Anaphylaxis and Allergy, McGill M. J. **10**:2, 1940; Studies on Blood Histamine in Patients with Allergic Disease, J. Clin. Investigation **20**:419, 1941.

be released at the same time. On the whole, however, the histamine theory is plausible. The injection of it into normal animals or human beings can mimic all the symptoms of allergy and anaphylaxis. It offers a reasonable explanation of the fact that a uniform symptom complex can be produced by a variety of exciting causes.

Is there any difference in the degree of reaction which different persons may exhibit toward histamine? In 1933, Rackemann, Simon and Scully [41] compared the skin tests with histamine on 85 asthmatic patients and 23 normal persons (nurses). Serial dilutions up to 1 to 1,000,000 were injected intracutaneously into the arm of each person. The reactions were a trifle larger in the asthmatic group, but the differences were not pronounced. More important is the old observation of Weiss, Robb and Blumgart [42] that patients with asthma are more susceptible to histamine than normal persons. They observed this during a study in which the flush which follows the intravenous injection of histamine was used as an index of the circulation time. In the patients with asthma, the flush appeared sooner and was much more pronounced than in the normal persons. Evidently, then, there is a little evidence than asthmatic persons are more susceptible to histamine than normal persons.

The next problem is to see whether histamine may be the mediating substance in conditions less well defined and which clinically depend on depletion, infection or intoxication. What else beside the antigen-antibody reaction will result in the release of histamine? Anrep and his co-workers [43] have shown that after exercise to produce hyperemia or after compression of the arm by a blood pressure cuff the histamine content of the plasma will increase as much as sixfold. Stead and Warren [44] observed that if histamine is injected into the brachial artery the capillaries of the forearm and hand become permeable, plasma is lost rapidly and venous blood from the area becomes concentrated. It is a temptation to use this last as an argument for the idea that other cholinergic influences can squeeze out histamine. In 1929, Kalk [45] observed

41. Rackemann, F. M.; Simon, F. A., and Scully, M. A.: Further Observations on the Nature of Allergy, J. Allergy **4**:498, 1933.

42. Weiss, S.; Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, Am. Heart J. **4**:664, 1929.

43. Anrep, G. B.; Barsoum, G. V.; Salama, S., and Souidan, Z.: Liberation of Histamine During Reactive Hyperemia and Muscle Contraction in Man, J. Physiol. **103**:297, 1944.

44. Stead, E. A., and Warren, J. V.: The Effect of the Injection of Histamine into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand, J. Clin. Investigation **23**:179, 1944.

45. Kalk, H.: Existence of a Histamine-Like Substance in Dermographism, Klin. Wchnschr. **8**:64, 1929.

that scratching the skin of a patient with dermographia will result in an increase of his gastric acid.

What is needed is a further study of depletion, including "nervous exhaustion" due to stress and strain, to find the mechanism by which these psychosomatic disturbances will produce their symptoms—obviously a complicated and difficult problem. Another paper by Rose [46] indicates the kind of studies which might be useful. He found that adrenalectomized rats could not inactivate histamine but that if the animals were fed adrenal cortex substance as desoxycorticosterone in fair-sized doses the function could be restored. This observation fits well with Selye's conception of the alarm reaction, to encourage the idea of adrenal deficiency as a basic factor. For the moment, it seems fair to allow the upper portion of the diagram in the chart to stand— that is, to assume that a variety of clinical states can result in the liberation of H substance.

Clinical treatment aimed at histamine might if successful provide further evidence that H substance was responsible for the symptoms in patients. Dragstedt [28] quoted Wells as suggesting that if histamine is important desensitization which inhibits one kind of a specific reaction ought to inhibit other reactions in the same animal at the same time. This statement, however, overlooks the fact that desensitization concerns nothing more than the specific antigen-antibody reaction and so merely removes the stimulus by which histamine is liberated. To inhibit histamine two methods have been devised. One concerns histaminase, a ferment to destroy histamine. The other concerns immunization against histamine itself.

In 1930, Best and McHenry [47] found that extracts of fresh tissue, particularly from the small intestine and kidney, could neutralize histamine in the test tube. In guinea pigs, Karady and Browne [48] first expressed the opinion that treatment with this histaminase could protect against anaphylactic shock, but later Rose and Browne [49] could not confirm the findings. In the treatment of patients the so-called histaminase has been found by many workers to be worthless. More recently, Lemley and Laskowski [50] have shown that in doses adequate

46. Rose, B.: The Effect of Cortin and Desoxycorticosterone Acetate on the Ability of the Adrenalectomized Rat to Inactivate Histamine, Am. J. Physiol. 127:4, 1939.

47. Best, C. H., and McHenry, E. A.: The Inactivation of Histamine, J. Physiol. 70:349, 1930.

48. Karady, S., and Browne, J. S. L.: Effect of Histaminase Treatment on Histamine and Anaphylactic Shock in Guinea Pigs, J. Immunol. 37:463, 1939.

49. Rose, B., and Browne, J. S. L.: Effect of Histaminase Pretreatment on Histamine Shock in Guinea Pigs, J. Immunol. 41:409, 1941.

50. Lemley, J. M., and Laskowski, M.: The Action of Histaminase in Vivo, Arch. Biochem. 6:115, 1945.

to produce a real effect the material is highly toxic. If some new substance of that kind could be discovered, perhaps on a different principle, that would be wonderful.

Immunization against histamine itself by repeated injections of it are not effective. Several papers on the subject were noted in the review of the literature on allergy for 1943.[7] Histamine is like its antagonist epinephrine—a substance which is present in the body normally and which has a well marked physiologic action. Is it surprising that a change in its quantity or in the resistance to its effects is hard to bring about? An exception to this sentiment is the result which Horton and his co-workers [51] have obtained in the special type of headache which they called "histaminic cephalalgia." Horton found that when histamine is well diluted with isotonic solution of sodium chloride and then injected intravenously at a rate of injection which keeps the dose just below the reaction level the results are good— almost spectacular in many cases. Whether this disease, which appears to be a local vascular disturbance due to a sort of intolerance to histamine, can be considered as comparable to the other, more typical, "asthmatic" symptoms remains to be seen. The physiology of histamine is complicated. Disturbances of the normal mechanism can be expected. Our knowledge of them is meager.

Histamine-protein combinations made by an azo linkage were first devised in 1943 by Fell, Rodney and Marshall,[52] who hoped to produce an immunity by the special preparation which they made. The new substance was found to be antigenic, so that in animals immunized to it precipitins of a typical sort developed. When, however, the serum from a rabbit immunized with histamine-azo-horse-serum was tested against histamine-azo-rabbit-serum or histamine-azo-casein, the reactions were not entirely clearcut. The specific element of the foreign serum was plainly evident, for the serum reacted better with the same material which had been used for immunization, but it reacted also with the other substances and that indicated that the histamine itself retained a function as a hapten. Animals immunized with these new substances did not lose any immediate histamine from their peripheral blood. They did, however, become resistant to anaphylactic shock, and the authors concluded that the previous treatment had resulted in an inhibition of the histamine and so caused their resistance to

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51. Horton, B. T.; MacAen, A. R., and Craig, W. M.: A New Syndrome of Vascular Headache: Results of Treatment with Histamine; Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:257, 1939. Horton, B. T.: The Use of Histamine in the Treatment of Specific Types of Headaches, J. A. M. A. **116**:377 (Feb. 1) 1941.

52. Fell, N.; Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes Synthesis and Immunologic Investigation: I. Histamine-Azoprotein, J. Immunol. **47**:237, 1943.

anaphylaxis.   In another experiment by Rodney and Fell,[53] the isocyanate derivative of histamine was coupled with despeciated horse serum globulin, and in this experiment again were a number of cross reactions easily demonstrated. This substance also could protect guinea pigs against the symptoms of anaphylaxis when they were immunized to it. The protection, however, was not perfect.

Cohen and Friedman [51] prepared histamine-azo-despeciated-horse-serum according to Fell's method and treated a number of patients with it, giving doses three to seven days apart for as long as three to twelve months. Precipitins to the injected complex were demonstrable at the end of treatment. When histamine was added to the precipitating serum and the mixture incubated for a time, the addition of the antigen complex no longer produced a precipitin reaction, for precipitin had been absorbed by the histamine. Moreover, when mixtures of serum from treated patients and histamine were applied to the skin of a normal subject and then tested with an electric current to drive the material in by the process of iontophoresis, no cutaneous reactions occurred. The histamine had been neutralized. In another paper, Cohen and Friedman [55] showed that the treatment of patients suffering from urticaria, allergic rhinitis and intrinsic asthma with histamine-azo-protein resulted in a diminution of their sensitiveness to histamine as applied by skin tests.

Meantime, M. Rocha e Silva [56] made five different compounds of histamine with amino acid and showed that when tested on the blood pressure of cats, guinea pig intestine or human skin there was little if· any pharmacologic activity; the histamine had been bound or captured by the compound. When later the compound was hydrolized in the presence of acid, the histamine was liberated so that the mixture would once more show its characteristic effects. Landau and ,Gay [57] added arginine and histidine to the Dale Bath and so prevented the reaction of the strip of guinea pig muscle to histamine. Also they showed that an injection of arginine can protect a guinea pig against an otherwise

53. Rodney, G., and Fell, N.: Histamine-Protein Complexes: Synthesis and Immunologic Investigation: II. B-(5-Imidazolyl Ethyl Carbamido Protein, J. Immunol. **47**:251, 1943.

54. Cohen, M. B., and Friedman, H. J.: Antibodies to Histamine Induced in Human Beings by Histamine Conjugates, J. Allergy **14**:195, 1943.

55. Cohen, M. B., and Friedman, H. J.: Immunity Against H-Substance, J. Allergy **15**:245, 1944.

56. Rocha e Silva, M.: Pharmacological Properties of Simple Compounds of Histamine with Amino Acids, J. Pharmacol. & Exper. Therap. **77**:198, 1943.

57. Landau, S. W., and Gay, L. N.: Influence of Certain Amino Acids on Histamine Reactions and Anaphylactic Reactions in Intestinal Strips of Guinea Pigs and in Intact Guinea Pigs, Bull. Johns Hopkins Hosp. **74**:55, 1944.

lethal dose of histamine, but it cannot protect the sensitized animal against death from anaphylactic shock.

More recently, Lehmann and Young [58] have recognized the antihistamine activity of diethylaminoethyldihydroanthracene carboxylate and showed that the injection of it can protect animals against anaphylactic shock with egg white. Also it can reduce the cutaneous reaction to histamine, and it can reduce the volume though not the acid concentration of the gastric juice when histamine is injected.

As for acetylcholine, the pharmacologic effect is much like that of histamine, but the fact that atropine, which is so effective in preventing the action of acetylcholine in animals, has no effect on the symptoms of allergy in human beings has been in itself a strong argument against the theory that acetylcholine plays an important part in allergy. Farber with Pope and Landsteiner [59] made a direct experiment; they removed the hearts, lungs and small bowels from normal guinea pigs and from other pigs sensitized to horse serum and divided each organ into two parts. One part was placed in plain Ringer's solution, while the other was placed in Ringer's solution to which physostigmine salicylate had been added. When horse serum was added to these mixtures, one might expect that acetylcholine as well as histamine would be released in each part of each preparation. In the part containing physostigmine salicylate, the cholinesterase would be inhibited so that the acetylcholine could be recognized by its typical physiologic effect on smooth muscle. The differences in the effects of the two parts with and without physostigmine salicylate would be a measure of the concentration of acetylcholine. In the actual experiment there was no evidence to indicate that more acetylcholine was released from the sensitized tissue than from the normal tissue. Meantime, in another experiment with the same sensitized tissues, the addition of specific serum resulted in the release of histamine, which was easily recognized in all preparations. More study of the histamine problem is needed. So far one can say that histamine appears to be a common denominator important in production of asthmatic symptoms, whether these are excited by allergic reactions or by other factors. The theory—particularly concerning these "other" factors—is not yet secure. The search for a treatment based on the histamine theory which will cure all the asthmatic symptoms at once is as difficult as it is exciting.

So far the best and most striking "treatment" of allergic diseases is that which occurs naturally or sometimes artificially in the form of

58. Lehmann, G., and Young, J. W.: The Anti-Histamine Activity of Diethylaminoethyldihydroanthracine-Carboxylate and Other Substances, J. Pharmacol. & Exper. Therap. **83**:90, 1945.

59. Farber, S.; Pope, A., and Landsteiner, E., Jr.: Role of Acetylcholine in an Anaphylactic Process, Arch. Path. **37**:275 (April) 1944.

fever.   Fever relieves asthma while the temperature is elevated and often for some time after.   Surgical operations relieve temporarily.   Jaundice relieves asthma while the jaundice is still present and for some time afterward.   Incidentally, in a recent paper Aikawa [60] pointed out that jaundice can also relieve the pain of arthritis.   How shall these effects be explained?   Are they concerned with the antigen-antibody reaction or with the liberation of H substance, or do these drastic circumstances result in an exhaustion of some other factor essential to the production of symptoms?   Are they related to the old observation of Manwaring [61] and others that the liver is an important organ in anaphylaxis and that exclusion of the liver by an Eck fistula can prevent anaphylaxis in sensitized dogs?

Individual symptoms will now be considered to see what is new about them and what problems they present.

263 Beacon Street.

60. Aikawa, J. K.: Hypersensitivity and Rheumatic Fever, Ann. Int. Med. **23**:969, 1945.

61. Manwaring, W. H.:   Intestinal and Hepatic Reactions in Anaphylaxis, J. A. M. A. **77**:849 (Sept. 10) 1921.

(To Be Concluded)

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